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The Effect of Interference on Reactivation of Spatial Memories in Reconsolidation Model by Using an Innovative Experimental Paradigm in Healthy Young Adults at the Behavioral Level

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The Effect of Interference on Reactivation of Spatial Memories in Reconsolidation Model by Using an Innovative Experimental Paradigm in Healthy Young Adults at the Behavioral Level

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Résumé

La mémoire déclarative est définie comme notre capacité à acquérir des faits et des événements qui font l'objet d'un souvenir conscient. Après la phase d'encodage, de nouvelles mémoires subissent des transformations hors ligne, qui permettent aux traces initialement labiles de se fixer dans la structure physique du cerveau; un processus appelé consolidation. Il existe également des preuves accumulées qu'une fois qu'une mémoire consolidée est réactivée ou récupérée, cette dernière passe par un processus de reconsolidation au cours duquel elle peut être dégradée, maintenue ou améliorée. Dans la présente étude, nous avons cherché à répondre à la question suivante: Les traces consolidées récupérées sont-elles susceptibles d'être perturbées par le même type d'information? Et quel serait l'effet de l'interférence sur différents tests de reconnaissance comparant les deux groupes. Méthode: Nous avons développé une tâche basée sur le travail de Sonni et al. (Sonni and Spencer 2015), où les sujets devaient apprendre à localiser 36 images d'objets du quotidien situées sur un écran d'ordinateur. 40 sujets en bonne santé (25,03 ± 3,66) ont participé à cette étude. Groupe 1: Interférence (20 sujets); Groupe 2: contrôle (20 sujets). Résultats: Nous avons constaté que l'administration de la matrice B après rappel de la première matrice (Groupe 1) interférait avec la reconsolidation de la mémoire, et augmentait ainsi significativement la quantité d'oubli observée lors de la reprise de la séance le Jour 3. En revanche, nous ne pouvions pas trouver un effet d'interférence dans le groupe de contrôle. Il y avait significativement plus de taux de fausses alarmes dans le groupe d'interférence. Nos résultats confirment l'hypothèse de reconsolidation de la mémoire déclarative, mais des travaux supplémentaires sont nécessaires pour déterminer si les substrats

neuronaux et neurophysiologiques qui interviennent dans la reconsolidation sont identiques ou différents de ceux impliqués dans la consolidation.

Mots-clés : mémoire déclarative, reconsolidation, interférence, recognition

Abstract

Declarative memory is defined as our capacity to acquire facts and events that are subject to conscious recollection. After the encoding phase, new memories undergo offline transformations, which allow the initially labile traces to become fixed into the physical structure of the brain; a process called consolidation. There is also accumulating evidence that once a consolidated memory is reactivated or retrieved, the latter goes through a reconsolidation process during which it can be degraded, maintained or enhanced. In the present study, we sought to answer the following question: Are retrieved consolidated traces susceptible to disruption by the same type of information? Method: We developed a task based on work by Sonni et al. (Sonni and Spencer 2015), in which subjects were required to learn the location of 36 everyday objects images located on a computer screen. 40 healthy subjects (25.03 ± 3.66) participated in this study. Group 1: Interference (20 subjects); Group 2: control (20 subjects). Results: We found that the administration of the matrix B after recall of the first matrix (Group 1) interfered with reconsolidation of the memory, and thus significantly increase the amount of forgetting seen in the retest session on Day 3. In contrast we could not find any interference effect in the control group. Our results confirm the reconsolidation hypothesis for declarative memory, but further work is needed to identify whether the neural and neurophysiological substrates mediating reconsolidation are the same or different from those involved during consolidation.

Keywords: declarative memory, reconsolidation, interference, recognition

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Liste des abréviations

ANOVA : ANalysis Of VAriance

AVLT : Auditory Verbal Learning Test

BD : Bipolar Disorder

CA1 : Cornu Ammonis in the hippocampus

CVLT : California Verbal Learning Test

DLPFC: DorsoLateral Prefrontal Cortex

ECT : ElectroConvulsive Therapy

EE : Episodic memory Encoding

EEG: ElectroEncephaloGraphy

fMRI : functional Magnetic Resonance Imaging

MPFC : Medial Prefrotal Cortex

MRI : Magnetic Resonance Imaging

MSL: Motor Sequence Learning

MTL: Medial Temporal Lobe

NREM : Non- Rapid Eye Movement

PET : Positron Emission Tomography

PFC: PreFrontal Cortex

PSQI : Pittsburgh Sleep Quality Index

REM : Rapid Eye Movement

ROC: Receiver Operating Characteristic

RULIT : Ruff Light Trial Learning Test

rTMS: repetitive Transcranial Magnetic Stimulation

SDT : Signal Detective Theory

SR : Semantic Memory Retrieval

SSS : Stanford Sleepiness Scale

SWS : Slow Wave Sleep

TMR: Targeted Memory Reactivation

TPT : Tactile Performance Test

TTT: Trace Transformation Theory

vmPFC: ventromedial PreFrontal Cortex

VOLT : Visuospatial Object Location Test

VSLT: Visual Spatial Learning Test

To my dearest mum for her unconditional love

To my beloved husband for his support

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Introduction

Forgetting is a common process in our everyday life, which, sometimes, may have important negative consequences. Forgetting occurs mainly because of the failure in the process of memory retrieval, not actually because the long-term memories are actually lost. Over the course of evolution, our brains have developed a remedy against forgetting. As such, acquired memories are stabilized and made resistance to interference through a processed called memory consolidation. This mnemonic process has been observed for different types of memory in various species during wake (Dewar, Alber et al. 2012) and sleep periods (Rasch and Born 2013). However, the consolidation process does not confer a permanent stability to memories, as evidenced by the fact that their subsequent reactivation (i.e. retrieval or reuse) makes them vulnerable again to interference (Nader, Schafe et al. 2000b). Accumulating evidence indicates that reactivated memories undergo a process of 're-stabilization', called reconsolidation, which is thought to be different than the initial consolidation process (Lee, Everitt et al. 2004; von Hertzen and Giese 2005; Maroun and Akirav 2009; Lee 2010).

Despite a growing number of studies investigating the reconsolidation process in humans, research on this topic has been plagued by a major limitation regarding the operationalization and assessment of reactivation, a crucial element in this model of memory reconsolidation. In a typical memory reconsolidation study design, part of the initially learned (encoded) material or of the learning context would be used during subsequent learning or testing session to reactivate the initially encoded memory traces (Hupbach, Gomez et al. 2007b). Notwithstanding the plethora of studies investigating the declarative memory, which have used

the concepts of reactivation, consolidation, and reconsolidation (Walker, Brakefield et al. 2003; Forcato, Burgos et al. 2007; Hupbach, Gomez et al. 2007a; Stickgold and Walker 2007), there is still much ambiguity regarding the way in which researchers define these concepts and operationalize them in their studies. For example, there are instances where the concepts of reactivation and reconsolidation have been used, but not explicitly operationalized or assessed. In studies using targeted memory reactivation procedures, perceptual cues (i.e. odors, sounds) are first associated with the information to be memorized during encoding and then are subsequently presented during sleep with the assumption that they will reactivate the encoded memories (Rihm, Diekelmann et al. 2014). Yet, despite a significant effect of this experimental manipulation on post-sleep memory performance, there is no actual assessment of the reactivation process. Similarly, in studies using interfering paradigms (Hupbach, Gomez et al. 2007a; Forcato, Rodríguez et al. 2011), researchers do not provide explicit assessments of memory reactivation, reconsolidation or even of the consolidation itself. As such, the phenomenon of reconsolidation and the effect of interference on this memory process are poorly understood.

Specifically, in declarative memory reconsolidation studies that used mostly free or cued recall tests to assess memory (Forcato, Burgos et al. 2007; Hupbach, Gomez et al. 2007a), given that the memory reactivation process per se or the strength of the initially encoded memory traces were not assessed, there is no distinction between items that were poorly encoded and actually forgotten versus those for which memory trace has become labile and was not consolidated again (i.e. reconsolidated). This limitation stems not only from the study design, but also from the choice of memory tests. By using just recall tests, which, by definition are binary in their response at the individual level, the memory strength cannot be really assessed.

Recognition tests, on the other hand, allow for the assessment of the overall memory strength via the discriminability d' parameter, yet, this measure may also depend on participant's choice of a conservative vs. liberal familiarity criterion (bias). For this reason, the combination of recall and recognition tests may be better suited to assess the strength of memory.

In the current study, we aim to address these methodological and conceptual gaps by using an innovative experimental paradigm and making use of both cued-recall and recognition tests of memory performance. As such, unlike previous studies, we will seek not only to operationalize, but also to provide evidence for the concepts of consolidation, reactivation and reconsolidation. The overall study objective is to provide direct evidence for the interference effect on memory reactivation during memory reconsolidation, at the behavioral level. Previous studies investigating memory interference during reconsolidation have only assumed that memory was reactivated (Sonni and Spencer 2015) and no study, to our knowledge, has assessed the effect of interference on consolidated versus non-consolidated items. For this reason, in the current study, we have developed a new spatial association memory task (Visual Learning Object Task) and we used both recall and recognition tests in an experimental design where the concepts of memory consolidation, memory strength and reconsolidation were explicitly defined and assessed.

Chapter 1 – Theoretical Context

1.1 – Declarative memory

Human memory is thought to consist of two systems, one that processes declarative or explicit memories, which are subject to conscious recollection (Squire, 2004), and one that treats non-declarative or implicit memories, such as motor skills (Figure 1.1). Declarative memory system is a distinct type of memory, which can be dissociated from other forms of memory both in healthy subjects (Metcalfe and Shimamura 1994), as well as in patients (Squire, Knowlton et al. 1993; Butters, Delis et al. 1995). Evidence for the existence of these two memory systems, and the fact that they may rely on different brain networks, has grown over the years since the first reported cases of amnesic patients (Scoville and Milner 1957; Corkin 1984). One of the earliest clinical example in this respect was the famous patient Henry Molaison, known as H.M., who underwent massive deficit in new learning after removal of the hippocampal formation and its associated medial temporal formations (Scoville & Milner, 1957). HM has shown impairments in declarative, but not in motor skills (Milner 1962; Milner, Corkin et al. 1968), thus providing evidence for the two systems and the dissociation in their neuronal substrates.

1.1.1 – Definition

Declarative memories are seen in the ability to bring events and facts to mind consciously, and to express them in various ways, but mostly verbal. They include episodic memories for events and experiences that are fixed in spatiotemporal context (including autobiographical memories), as well as semantic memories for facts and knowledge that are encoded independently of the context associated with them (Tulving, 1984).

Declarative memories, in general, are encoded intentionally and explicitly. They are learned fast, but are also easy to forget (Wixted, 2004), in opposition to semantic memories, which need repetition, but their encoding usually lasts longer (Winocur, Moscovitch, & Bontempi, 2010).

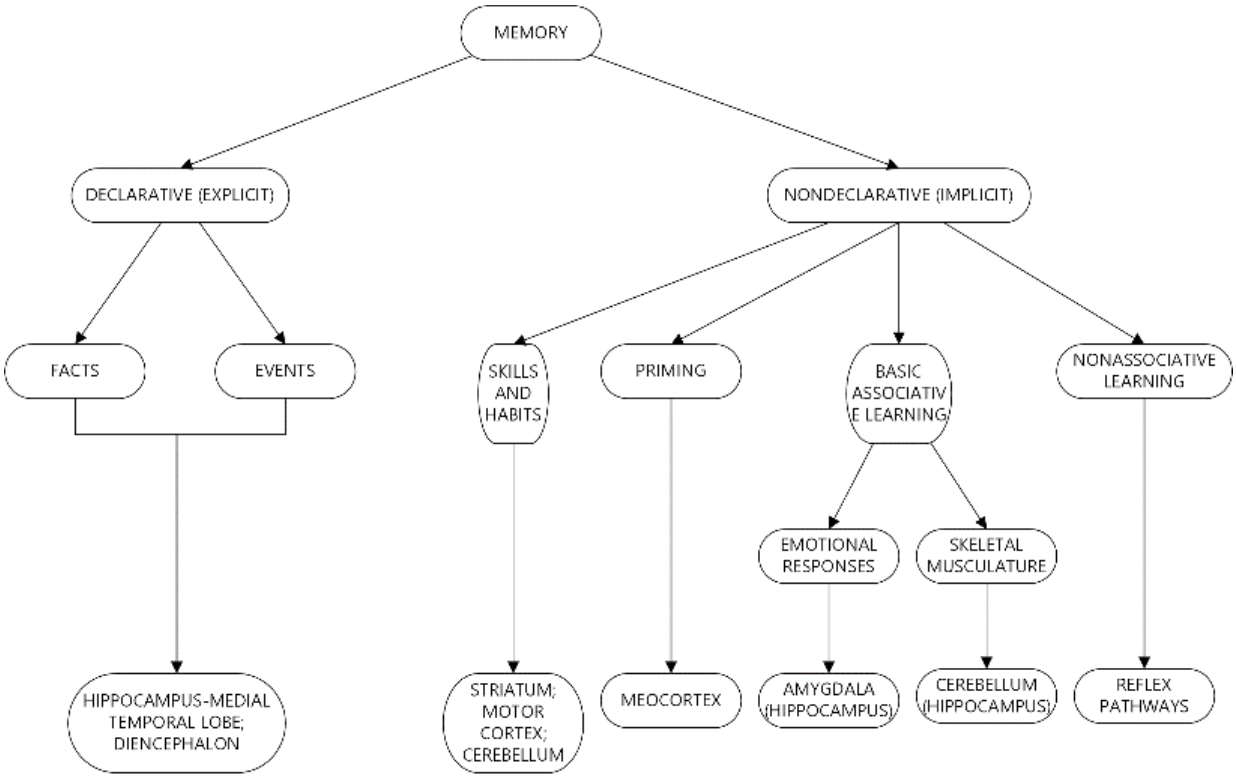

Figure 1.1. General classification of memory

1.1.2 – Characteristics

Declarative memories can be acquired immediately by exposure to just a single event or from exposure to repeated experiences. The uptake of new information predispose it to 'overwriting' and erasing of the old memories (Stickgold 2002). The retrieval of all types of declarative memories is explicit in nature and is typically made with awareness (Tulving 1985). The two main types of declarative memories can be classified based on the presence of time and

space dimensions. Episodic memories are those which contain these dimensions, as opposed to semantic memories for which these dimensions are lacking or are unimportant (Schacter and Tulving 1994).

Episodic memory refers to the encoding, storage and retrieval of information about events experienced by the individual. This type of memory is often associative by nature, meaning that when someone remembers an event, all features associated with that event, be it central or peripheral, could be recalled or recognized, such as people, time and place. This type of memory crucially depends on the functioning of hippocampus and its connection to the cortex (O'Reilly and Rudy 2000). Contrary to their episodic counterpart, the semantic memory can be long-lasting and resistant to forgetting (Tulving 2002).

One of the first memory classifications was based on the storage type and the longevity of the stored information, the memory, which classified it into three categories (Waugh and Norman 1965; Atkinson and Shiffrin 1968). The shortest-lived one is sensory memory, which consists of different encoded information acquired directly through different sensory modalities (visual, verbal, audial, tactile, etc.). The second category refers to short-term memory, which contains the information encoded and retained for a duration ranging from seconds to minutes. The third category is long-term memory, which is thought to contain information that is encoded and stored for very long periods, often permanently.

A specific information may pass from the sensory to short-term and then to long-term memory storage based on the depth of processing. The more processed and rich the information, the more likely it is that it will be retained for longer periods (Craik and Lockhart 1972). For example, an emotionally-laden information or heightened attention at the moment of encoding

will facilitate the long-term storage of the information and will ease its retrieval. In addition to emotion or attention, there are other external and internal factors, which can affect memory performance, such as the physical conditions, motivation, tiredness, information processing speed, and testing conditions (Ganor-Stern, Seamon, & Carrasco, 1998).

1.1.3– Behavioral testing of declarative memory

Based on the type of stored information; its modality (verbal, visual) and its timeline (immediate, remote), the memory can be assessed using different tests; in fact, there is not a single universal test to evaluate declarative memory. For instance, verbal declarative memory can be assessed by tests using verbal automatisms, letters and digits, and words. There are interference-learning paradigms such as the Auditory Verbal Learning Test (AVLT) (Rey 1964) or the California Verbal Learning Test (CVLT) (Delis, Kramer et al. 1987). The list of words are used in both of these tests to examine variety of memory measures like short-term and long-term free recall and recognition. The association between two pairs of items stimulus and response are tested by the paired associate word learning test (Calkins 1894). Logical memory test such as Wechsler's logical memory (Wechsler 1945) has seven subtests and assess memory in different time points, either immediately or delayed. There exist other tests for evaluating verbal recall such as story recall.

Visual learning can be tested by the Visual Spatial Learning Test (VSLT), the Heaton Figure Memory Test; the visual stimuli in this test being driven from Wechsler Memory Test (Heaton, Grant et al. 1991). The Rey Complex Figure Test gives information on visuospatial recall and recognition memory (Meyers and Meyers 1995). This test also measures the

immediate visual recall as well as long-term visual recall. These visual tests were developed to lessen the verbal effect when assessing the memory.

Spatial declarative memory has been examined by a variety of tasks in which spatial layouts during navigation or spatial locations for different objects are learned. Regarding memory for spatial location, one of the tasks often used in the literature is the Visuospatial Object Location Test (VOLT). In this experimental paradigm, participants are required to learn the location of pairs of objects presented in a two-dimensional location matrix (Rasch, Büchel et al. 2007a; Diekelmann, Biggel et al. 2012). They are then provided with one element of the pair and have to locate the second object. The task involves associative memory and relies on the medial temporal lobe structures (Sommer, Rose et al. 2005).

Declarative memory tests can also be classified based on whether they assess the retention of declarative information over different timelines (short-term, long-term). Immediate recall tests assess the working and/or short-term memory before its consolidation. Delayed memory tests can be used to evaluate long-term memory in clinical population, such as in patients with retrograde amnesia. These tests can assess the recall and/or recognition of public events and famous people, personal-autobiographic memory, and the ability to remember one's history (Lezak 2004).

In general, based on the means by which encoded information is retrieved, there are two main types of memory tests: recall and recognition. Recall tests can be administered with or without cues and they are more difficult than the recognition tests because the individual has to internally generate the encoded information. In contrast, recognition tests are easier because the individual is presented with old and/or new information and is asked to indicate whether it was

encoded before or whether it is familiar or not. Performance at this type of tests is dependent on the subject's strength of familiarity with the item (Wickelgren and Norman 1966). Also, less information is needed for a successful recognition than a successful recall (Postman 1963). It is generally understood that well encoded information will be both recognized and recalled, whereas the weakly encoded information may just be recognized, but not recalled. (Tversky 1973). It was demonstrated that integration of details during encoding phase leads to enhancement of recognition, which is evidence of a relationship between encoding and recognition. Therefore, a comparison of the performance at recall and recognition tests may be indicative of the memory strength.

1.1.4 – Brain substrates of declarative memory

Different types of memories, corresponding to multiple memory systems, are thought to be stored and/or processed by different brain regions. In neuropsychology, declarative and non-declarative memory systems are distinguished depending on the critical involvement of regions located in the medical temporal lobe, particularly of the hippocampus, especially during the encoding or the acquisition memory phase (Squire and Zola 1996). Tulving provided evidence for different brain memory systems related to episodic and semantic memory, which are, nevertheless, interacting to each other (Tulving 2002). To this end, Nyberg and colleagues used functional imaging to identify the neural substrate for Episodic memory Encoding (EE) and Semantic memory Retrieval (SR) (Nyberg, Cabeza et al. 1996). They reported that the left temporal region and hippocampus were involved for EE, whereas the posterior inferior parietal region was activated in SR. In inferior prefrontal cortex, EE was associated with increase activations in its ventral regions, whereas the activations in posterior regions were associated to

SR. Other imaging studies also showed the involvement of hippocampus in the encoding of the episodic memories (Montaldi, Mayes et al. 1998), in association with its known cerebral cortex projections, including the prefrontal cortex, whereas semantic memories formation was reported to be associated with increased activity in the perirhinal cortex (Davies, Graham et al. 2004).

Evidence that there are different brain systems for short-term declarative and non-declarative memories emerged from several famous clinical cases of amnesia. Three of these cases (patients H.M., N.A., and R.B.) revealed the importance of the integrity of midline diencephalon and medial temporal lobe structures, specifically the hippocampus (Figure 1.2), in the formation of declarative memories. In the patient H.M., for instance, a resection of bilateral medial temporal lobe including the amygdala, hippocampal gyrus, and anterior two-thirds of the hippocampus was done for treating his seizure. After his surgery, H.M. experienced anterograde amnesia that is he lost his ability to learn new short-term declarative memory despite the fact that his other cognition functions, as well as the capacity to form procedural memory, were unimpaired (Scoville and Milner 1957). The patient N.A. displayed severe anterograde amnesia for declarative memory after his head injury. The damage was in thalamus area and the medial temporal lobe, based on the MRI anatomical studies. His symptoms were similar to those of H.M. in that he retained the ability to learn new procedural skills (Purves, Augustine et al. 2004). Brain biopsy for the case of R.B., who showed moderately severe anterograde amnesia after ischemic attack, unveiled only bilateral hippocampal lesions although other regions were normal. He was the first human amnesic patients who provided evidence that hippocampal lesions are enough to produce declarative memory impairment. That case indicated that other brain regions like amygdala may not be critical for encoding of declarative memory (Squire and Zola 1996).

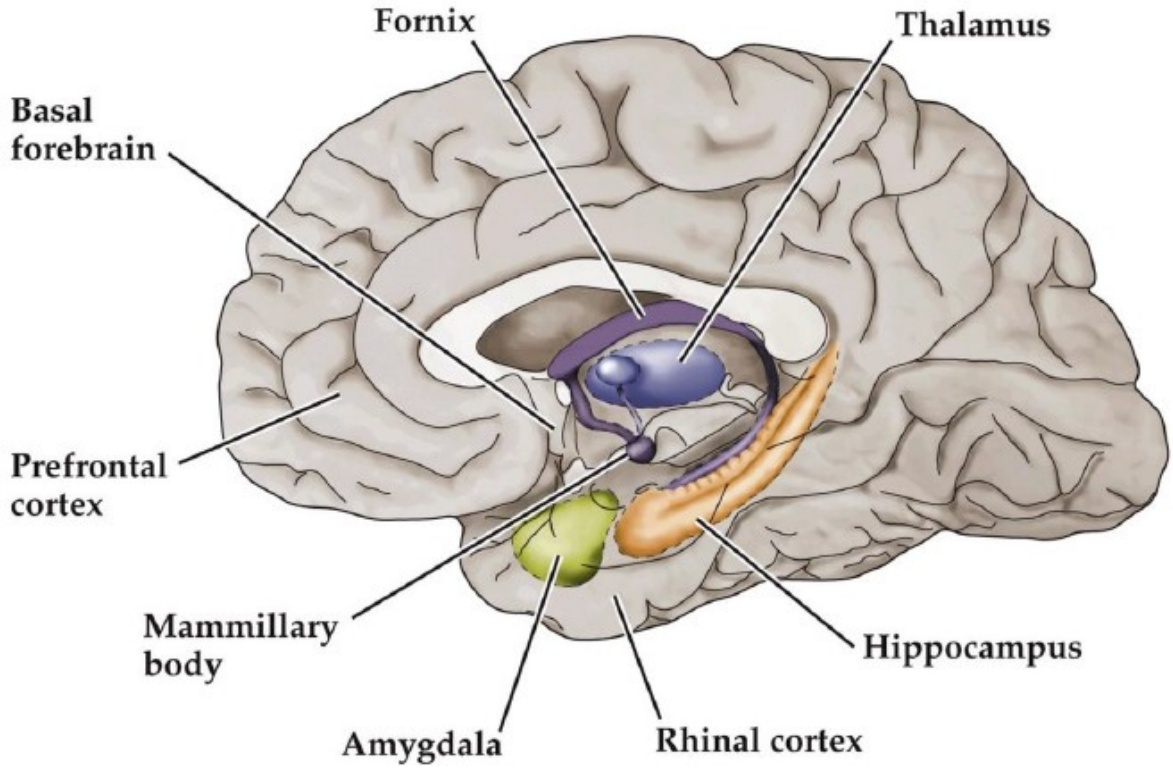

Figure 1.2: Brain systems responsible for encoding declarative memories (Bear, Connors et al. 2007)

Notwithstanding the memory impairments seen in those amnesic patients, they could still recall distant memories before the accident; all of these indicate that long-term memories are stored somewhere else in the brain, in the parts that were not affected by the lesion. In fact, evidence from electroconvulsive therapy (ECT) and neuroimaging studies suggest that these long-term memories are stored in the cerebral cortex. For instance, MacQueen and colleagues studied declarative memory in three groups of subjects, one group who received ECT as a treatment for bipolar disorder (BD), another group of BD patients who had not received any treatment and a group of healthy subjects. They found verbal memory deficits in subjects who received ECT for at least 6 months before assessment compared to the other two groups (MacQueen, Parkin et al. 2007). Based on previous evidence that ECT affects specifically

cortical regions, the same authors proposed that these regions were associated with long-term memory formations. In a study investigating the neural substrates involved in a free recall task, Fletcher and colleagues used positron emission tomography (PET) in healthy subjects to demonstrate that the retrieval of verbal material was associated with increased activation in right prefrontal and medial parietal cortices (Fletcher, Shallice et al. 1998). In another PET study employing a paired association task to identify brain regions related to episodic memory encoding and retrieval found that retrieval was specifically associated with activation in the right prefrontal cortex (Shallice, Fletcher et al. 1994). Brain regions associated with performance at recognition tests were examined in another PET study and they included the right prefrontal cortex, left anterior cingulate, and cerebellum (Nyberg, Tulving et al. 1995).

These findings were also confirmed by several imaging studies using functional Magnetic Resonance Imaging (fMRI), an imaging technique measuring changes in blood oxygenation associated with neural activity. For instance, Stern and colleagues showed activation in hippocampus during encoding of a complex visual scene (Stern, Corkin et al. 1996) for items which were correctly identified in a post-scan recognition test. This effect was replicated in later studies using different types of stimuli, such as complex visual images (Brewer, Zhao et al. 1998) and verbal items (Wagner, Schacter et al. 1998). Kirrchhoff and colleagues showed more lateralized hippocampal activation for encoding of verbal stimuli compared to pictures (Kirchhoff, Wagner et al. 2000). Several other fMRI studies demonstrate the involvement of other regions in the encoding process, including the inferior prefrontal, the parietal (Burgess, Becker et al. 2001; Byrne, Becker et al. 2007), and the retrosplenial cortex (Epstein 2008). Hippocampal involvement in recognition of words and pictures was reported in many fMRI studies (Wheeler and Buckner 2004; Eldridge, Engel et al. 2005; Montaldi, Spencer

et al. 2006; Cohn, McAndrews et al. 2009; Rugg, Vilberg et al. 2012). Wais and his colleagues classified memories into strong and weak based on the shape of Receiver Operating Characteristic (ROC) as a function of strength of memory (Wais, Wixted et al. 2006), Furthermore, Wixted and Squire used that classification of memory in their study and showed the activation of hippocampal structure in retrieval of strong memories (Wixted and Squire 2011), whereas that of weak memories was supported by the activation in perirhinal cortex (Wais 2008). Beside the functional dissociation between hippocampus and surrounding structures, there is also evidence demonstrating a functional dissociation within hippocampus, in which the posterior portion of hippocampus is involved in retrieval, whereas the anterior part is involved in encoding (Spaniol, Davidson et al. 2009; Poppenk, Evensmoen et al. 2013).

In addition to hippocampus and surrounding structures, several fMRI studies showed increased activation in dorsolateral pre-frontal cortex (DLPFC), dorsomedial parietal cortex, dorsal posterior parietal cortex, posterior cingulate and precuneus during recognition memory tests (Konishi, Wheeler et al. 2000; Rugg and Henson 2002; Kim 2013; Nelson, McDermott et al. 2013). Regarding the memory retrieval process, one of the first regions to be linked to this process was the prefrontal cortex (PFC) (Buckner, Goodman et al. 1998; Wagner, Schacter et al. 1998); however, activation in the parietal cortex during memory retrieval tasks has also been shown in many fMRI studies (Shannon and Buckner 2004; Wagner, Shannon et al. 2005; Vilberg and Rugg 2008; Hutchinson, Uncapher et al. 2009). More specifically, Nelson and his colleagues demonstrated that the activation in left lateral parietal cortex was specific for old versus new items in the recognition test (Nelson, McDermott et al. 2013). In addition to investigating the neuronal substrate subtending various memory processes, in general, there are researchers who have uncovered the neuronal correlates specific to particular memory types.

For example, Morris Moscovitch, a neuropsychologist at the University of Toronto, has conducted research on declarative and episodic memory and has proposed the Trace Transformation Theory (TTT) describing the reorganization of patterns of neural activity in relation to the memory quality, specifically its transformation from a memory trace that is perceptually detailed or context-specific to one that is more schematic or context-general. In a series of studies, Moscovitch and his team demonstrated that an episodic memory trace undergoes a transformation during which its schematic features are represented cortically, whereas both fine and coarse contextual and perceptual details characterizing the original experience continue to be represented in the hippocampus (Nadel and Moscovitch 1997; Moscovitch, Cabeza et al. 2016; Sekeres, Winocur et al. 2018a; Sekeres, Winocur et al. 2018b). All together, these studies provide evidence that different parts of the brain are involved in different memory processes, such as encoding, consolidation and retrieval of declarative memories. Moreover, they seem to indicate that the medial temporal lobe regions are mainly involved in the short-term memory formation, whereas other cortical regions seem to play an important role in their consolidation and long-term retention.

1.1.5 – Information processing models of declarative memory

Information gathered from different senses are stored in the brain for later retrieval, suggesting that the information undergoes different transformations between encoding and retrieval. In the human memory research domain, the information processing models posit that there are different processes that subtend the information processing in sensory, working, and long-term memory (Craik and Lockhart 1972). Many information processing theories have been developed over the years in this regard, but in the current thesis, we will focus on two primary

models: Baddeley's model of working memory (Baddeley and Hitch 1974) and the two-stage model of memory (Atkinson and Shiffrin 1968).

Baddeley proposed a three-component model for working memory, instead of a unitary model, in which visual and spatial information, such as pictures and maps, are processed in a visuospatial sketchpad, while verbal information (i.e. words and numbers) are processed in a phonological loop (Baddeley and Hitch 1974). In support of this model, Baddeley and colleague asked subjects to perform a dual-task (encoding verbal material while repeating back a sequence of digits) in order to assess the capacity of the short-term memory. The rate of errors for the verbal material was low and the authors did not find any reductions in the short-term memory capacity, which was assessed by the performance for digit repetition (Baddeley and Hitch 1974). Based on these findings, Baddeley and Hitch proposed the existence of different subsystems for storing different types of information. According to their model, these consist of a central executive, a phonological loop and a visuospatial sketchpad. The most important part of this ensemble is the central executive system, which is involved in directing the attention to the component that needs it the most, while suppressing the one that is not needed or should be ignored. It takes the information from two storing subsystems; phonological loop and visuospatial sketchpad. Later, Baddeley added a new component to this system namely the episodic buffer, which acts as a connector between long-term memory and the components of working memory (Baddeley 2000) (Figure 1.3).

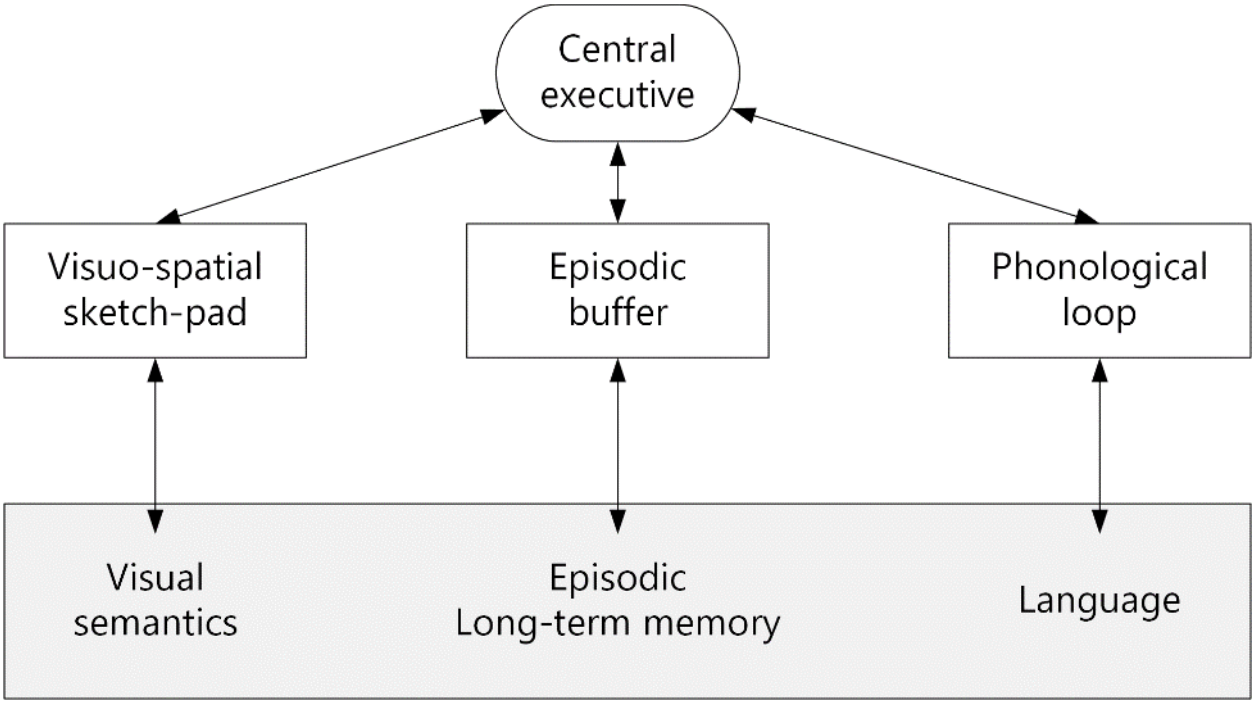

Figure 1.3. Three-component model of working memory based on Baddeley model 1974

The two-stage model of memory was developed by Atkinson and Shiffrin (Atkinson and Shiffrin 1968). This model proposes that there are three basic types of memory: sensory, short term, and long-term memory. Sensory registration of information, also called the sensory memory, is the first step of storing information that is collected through different five senses (sight, smell, hearing, touch, and taste). This storage lasts as long as a few seconds and could happen without paying attention to the stimuli (Neisser 1967). The memory can be further processed and stored within short-term and long-term memory storages. The information in short-term memory is stored for up to 30 seconds, while, theoretically, the information in long-term memory should last forever. Short-term memories are unstable and vulnerable to interference; such is the case with the newly acquired information. Over time, the information is integrated in the long-term memories both passively or actively. Subsequent imaging studies

confirmed Atkinson and Shiffrin's model, specifically the process by which the information is initially encoded into a short-term store, like hippocampus, and then gradually transferred to a long-term storage (i.e., the neocortex) (Marr, Willshaw et al. 1991). Depending on the acquired information, the time needed to be encoded in the long-term memory could range from a very short interval to a long period (Tse, Langston et al. 2007; Wang and Morris 2010). There were also lesion studies that provided evidence for the Atkinson and Shiffrin's two-stage model of memory. For example, lesion of the hippocampus decreases the ability to gain new declarative memory while leaving intact the old memories, which are thought to be stored in other parts of the brain (Corkin 2002; Frankland and Bontempi 2005). These findings suggest that hippocampus may be the site for short-term memory formation, with other parts of the brain being the site for the information already stored in the long-term repository.

1.2 – Information Processing in Declarative memory

Different processes describe the transformations of the information in declarative memory, from the initial encoding to the final stages of retrieval.

1.2.1 – Encoding

The perception of stimuli, including attending to them and their processing, leads to the formation of new memory traces in the brain (Craik & Lockhart, 1972). This process is called encoding and the memory representation formed during this stage is highly sensitive to perturbing factors.

During encoding, the information processing is done differently depending upon the instructions and the task at hand; it can be influenced by the degree of attention and the extent

of elaboration on its meaning, as well as the association between the old and new information, which can vary from shallow to deep processing. To answer the question as to what other factors can influence on high level of retention, Jacoby and his colleagues used the difficulty of making decision in their experiment (Jacoby, Craik et al. 1979). In their study, they asked subjects to memorize a list of 40 words of which half were misspelled. The subjects had to write down the correct version of those words. The results demonstrated that the level of difficulty in making decision during encoding phase is positively related to the distinctiveness of the memory traces, more than to the depth of processing and would be more discriminative during retrieval. There are two phenomena, which describe the processes of encoding of declarative memories, the generation and spacing effects. Regarding the generation effect, in an experiment comparing the memory performance for a list of words under two conditions (words generated versus just read by the participants), the experimenters found significantly higher scores in a variety of retrieval tests including cued and uncued recognition, free and cued recall, in the Generator than in the Read group (Slamecka and Graf 1978). Spacing effect is observed in studies when the same material is presented over separate sessions with intervals (spaced presentation) versus all at once (i.e. massed presentation). This effect, which was first recognized by Ebbinghaus (Ebbinghaus 1885) at short retention periods, is seen as improved performance on memory retrieval for the spaced vs. massed presented material. In another study in which participants had to learn 140 new faces under spaced vs. massed conditions, the results demonstrated that the recognition test performance was better in spaced rather than massed condition (Wang, Xu et al. 2017). Taken together, all these studies provide evidence for better memory retention if information is presented in a spaced fashion during the encoding phase. Thus, a large body of research has indicated that the way information is encoded influences the subsequent access to

that information and that the best retention occurs when processing is deep (Craik and Lockhart 1972).

Several imaging studies evaluating the neural substrate of the encoding phase showed that the medial temporal lobe and more specifically the hippocampus and inferior prefrontal area play a role in this process (Wagner, Schacter et al. 1998; Otten and Rugg 2001; Paller and Wagner 2002; Morcom, Good et al. 2003). For example, in one fMRI study, the authors examined the activation of hippocampus during encoding and retrieval of words and they discovered significant activation in that region in both of these conditions (Greicius, Krasnow et al. 2003).

1.2.2 – Offline transformation: Consolidation, the stabilization of labile memory

The freshly encoded and labile memory traces undergo changes at the molecular, cellular, and system levels that occur automatically and outside of awareness. As a result of these changes, these traces are stabilized and are converted into a long-term memory. This process of stabilization and becoming resistant to interference is called memory consolidation (Müller and Pilzecker 1900) see (McGaugh 2000; Dudai 2004) and it happens offline (i.e. after the stimuli were presented). In addition to stabilization, memory consolidation may also be understood as an integration process during which the new information is linked to or integrated into the preexisting knowledge network. Yet there are not many studies that have investigated this specific aspect of the consolidation process. In contrast, the stabilization process was examined extensively by using different types of stimuli such as words recall, word-pair, and

object location learning tasks (Rasch, Büchel et al. 2007b) and has been seen in different species (McGaugh 2000; Kandel 2001).

From the point of view at which level the consolidation takes place, there are two types of consolidation processes: cellular/synaptic and brain system level/systemic. The changes occurring at the intracellular neuronal level that encode the memory and facilitate the long-term information retention via protein synthesis are called synaptic or cellular consolidation. Synaptic consolidation exists in all species from invertebrates to vertebrates (Kandel, Dudai et al. 2014). This type of consolidation is characteristic to all types of memories, including declarative and non-declarative, is seen in the early hours of learning (Dudai 2004; Frankland and Bontempi 2005) and it is considered to be a fast process. In contrast, systemic consolidation is the second type of consolidation, which refers to the long-term memory stabilization and is seen for the types of memories that are typically dependent on hippocampus. Systemic consolidation may persist from days to years; during this time, the hippocampus dependent memories are rearranged over distributed brain circuits (Dudai and Morris 2000). This distributed model in which hippocampal-dependent memories are processed in a network of cortical regions was confirmed by several fMRI studies (Takashima, Petersson et al. 2006; Gais, Albouy et al. 2007). For instance, Takashima and his colleagues tested this model by using a face-location association task with two different time delays and showed a decrease in hippocampus activity for those who studied face-location associations 24 hours before imaging (remote memories), as compared to those who studied them 15 minutes before (recent memories). In contrast, the neocortex activity showed the opposite pattern, increasing as time passed. It was found that systemic consolidation occurred in both semantic and episodic memories, be it spatial or non-spatial (McGaugh 2000).

Traditionally, it was believed that consolidated memories are immutable and they could not be interfered with (Dudai 2004). However, numerous studies showed that administration of different types of manipulations after encoding could impair or enhance subsequent memory retrieval (McGaugh 2000; Wixted 2004), that those manipulations were time-dependent (Chorover 1976; McGaugh and Gold 1976) and, depending on the memory system, that they may last from days to years (Dudai 2012).

Since the concept of consolidation was proposed, a large body of research has indicated that sleep plays an important role in consolidating memory traces. There is a time dependency for the effect that sleep has on memory performance, such as that if sleep occurred immediately after learning, the memory performance is improved. For example, one study showed that having sleep 3 versus 10 hours after learning verbal materials resulted in better memory performance, indicating that sleep had a protective effect on forgetting and against interference when occurring within a few hours of learning, regardless of the time of the day (Gais, Lucas et al. 2006). Other studies provided evidence for the fact that sleep protected the declarative memory traces from subsequent associative interference, which occurred immediate after learning (Ellenbogen, Hulbert et al. 2006), as well as for the role of sleep in reducing forgetting of newly encoded information, i.e. retroactive interference (Rasch and Born 2013). There is also evidence that different types of memories are consolidated during specific sleep stages (Maquet 2001; Smith 2001; Gais and Born 2004a; Rauchs, Desgranges et al. 2005; Marshall, Helgadóttir et al. 2006). For instance, Rapid Eye Movement (REM) sleep has been shown to contribute to the consolidation of the memories that are not dependent to hippocampus, such as procedural memories (Plihal and Born 1997; Stickgold 2005) and the generalization of object recognition learning (McDevitt, Rowe et al. 2014). In contrast, the early stages of nocturnal sleep, which

contain many Slow-Waves Sleep (SWS), seem to be important in the consolidation of declarative memory (Plihal and Born 1999a; Smith 2001; Walker and Stickgold 2006).

Ellenbogen and colleagues have demonstrated the beneficial effects of sleep in memory consolidation expressed as resistance against future interference for verbal memories (Ellenbogen, Hulbert et al. 2006; Ellenbogen, Hulbert et al. 2009). The resistance of declarative memory against future interference was studied by using paired-associate words, mirror-tracing skills (procedural memory) and mental spatial rotation task, and by correlating the memory performance with time spent in slow-wave sleep (Plihal and Born 1997; Plihal and Born 1999a). There is also evidence at the molecular level that provides support for the role and the importance of early sleep for the consolidation of declarative memory (Plihal and Born 1999b; Gais and Born 2004b).

In addition to slow-waves, the other type of oscillatory sleep activity that was found to be related to memory consolidation is sleep spindles. These are short bursts (< 3 seconds) of 10-16 Hz oscillatory activity seen during stages 2 and 3 of NREM sleep (Antony, Schönauer et al. 2019). A large body of research has provided evidence that various spindle characteristic (i.e. density, amplitude, duration etc.) have been associated with the consolidation process of both declarative and procedural memories, expressed as post-sleep improved performance (Barakat, Doyon et al. 2011; Barakat, Carrier et al. 2013; Laventure, Fogel et al. 2016; Fogel, Albouy et al. 2017; King, Hoedlmoser et al. 2017; Boutin, Pinsard et al. 2018; Laventure, Pinsard et al. 2018; Schönauer 2018; Antony, Schönauer et al. 2019).

1.2.3 – Reactivation

Memory reactivation refers to the process by which memory traces are brought from an inactive to a temporary active state, usually by re-exposure to the original or to related information that was present at encoding (Lewis 1979), such as cues or reminders that could be internal or external. Shortly after reactivation, memories are thought to be malleable and fragile, similar to their state immediately after training (Nader and Hardt 2009). That malleable state after reactivation is essential for updating contextual memory content (Lee 2010; Alberini 2011). However, this destabilization or fragilization of memory traces makes them more susceptible to modification, as evidenced by clinical studies that found recovery from amnesia after exposure to training cues (Miller and Springer 1972). In studies investigating memory reactivation, cues or reminders associated with the original material to be memorized are thought to reactivate the memory traces. For instance, Hupbach and colleagues (Hupbach, Gomez et al. 2007a) used a list of objects to be learned by subjects and the objects from the list were placed in a basket after the experimenter showed each item to the participants, one by one. Two days after the initial learning session, the subjects were either reminded or not about the experiment by being shown the same basket that was used initially, but which was empty, after which they had to learn a second list of objects. There were three groups in their study; reminder, no reminder and interference control. High number of intrusions from a second list in free recall of first list was shown just in the reminder group, whereas there were no intrusions from the first to the second list in the free recall test on the third and last day of experiment, for both the reminder and no reminder groups, an evidence for the reactivation process per se, as well as for the update of information in memory after being reactivated by reminders.

The memory reactivation can occur both in the waking state, but also during sleep (Stickgold 2005; Rasch, Büchel et al. 2007a; Diekelmann and Born 2010). Past research supported the active role of sleep in long-term memory formation and consolidation which is purported to arise from repeated reactivation of new memory traces or representations during sleep as indicated in human studies, both in the procedural and declarative memory domains (Ellenbogen, Hu et al. 2007; Rasch and Born 2007; Rasch and Born 2008; Walker 2010; Diekelmann, Büchel et al. 2011; Lewis and Durrant 2011). Experimentally, this process is investigated using a Targeted Memory Reactivation (TMR) paradigm using olfactory and auditory cues during learning and sleep (Rasch, Büchel et al. 2007a; Rudoy, Voss et al. 2009; Oudiette and Paller 2013). For instance, in a study investigating the consolidation of declarative and procedural memories, Rasch et al. showed the reactivation of both declarative and procedural memory traces during sleep by presenting the same odor during slow-wave sleep as that used during the training session (Rasch, Büchel et al. 2007a). They did not observe any evidence for enhanced memory consolidation in the group who had odors present only during sleep, whereas in the group, in which the odor was presented both during learning and during sleep, there was an increase in retention of declarative, but not procedural memories, which would suggest that there was a reactivation of the declarative memory trace during slow-wave sleep that facilitated the consolidation process.

The TMR paradigm can be used not only to demonstrate the memory trace reactivation during sleep, but also to test whether this process occurs in specific sleep stages or during specific sleep oscillatory activity. To this end, Laventure et al. used TMR with odor cues to show a higher gains in the performance (motor learning consolidation) in participants were conditioned with the odor during training and re-exposure to the same odor during stage2 NREM

sleep, as compared with participants who were not exposed to odors or had the odor cues presented during REM sleep (Laventure, Fogel et al. 2016). Similar evidence was provided by studies investigating human episodic memory, such as the TMR study conducted by Diekelmann et al. in which the reactivation of declarative memory traces (visuo-spatial associations) was demonstrated by increased retention of memories after odor cues presented during learning and SWS, as compared to participants who had odor cues presented during wakefulness (Diekelmann, Buchel et al. 2011).

In recent years, several neuroimaging studies in humans have demonstrated that the reactivation of memory traces occurs during specific sleep oscillations, such as the sleep spindles for procedural memory. For instance the activation of striatum, both during learning, as well as time-locked to spindles during nocturnal sleep following the motor sequence learning task was shown in a study using simultaneous electroencephalographic and functional magnetic resonance imaging (EEG-fMRI) recordings (Fogel, Albouy et al. 2017). Moreover, the EEG spectral analysis of the same data has shown that during NREM2 sleep spindles the reactivation and functional synchronizing of subcortical and cortical networks correlated with the consolidation of the motor memory seen post-sleep (Boutin, Pinsard et al. 2018). In addition to procedural memory, the same EEG-fMRI methodology has been used in combination with a declarative memory task (learning of sequences of faces) known to elicit increased activation in the fusiform gyrus during encoding. The authors found a significant correlation between the fusiform gyrus activity and larger responses during sleep, which was synchronized by the fast spindles (Jegou, Schabus et al. 2019).

Despite a growing number of studies investigating or using the reactivation process in memory consolidation, it is not well-known the extent to which there is any difference between

the sleep-related memory reactivation and that triggered by reminders or by cues during wakefulness (Diekelmann, Büchel et al. 2011).

1.2.4 – Memory reconsolidation

The process of memory consolidation does not always lead to memory traces that are fixed or immutable, as it has been extensively shown by past studies demonstrating that many memory types could be changed, both in terms of encoding strength, as well as in terms of content, after acquisition (Walker, Brakefield et al. 2003; Forcato, Burgos et al. 2007; Hupbach, Gomez et al. 2007a; Hupbach, Hardt et al. 2008; Forcato, Argibay et al. 2009; Hupbach, Gomez et al. 2009; Forcato, Rodríguez et al. 2010; Forcato, Rodríguez et al. 2011; Hupbach, Gomez et al. 2011). After reactivation either by a specific reminder or by active retrieval, consolidated memories can become labile again and they are vulnerable to interferences like amnesic agents (Morris, Inglis et al. 2006). This vulnerability, however, decreases over time (Nader and Hardt 2009), suggesting that there is a re-stabilization of labile memories, via a process called reconsolidation. This phenomenon is thought to be different from the initial memory consolidation, even though these two processes seem to share several cellular and molecular mechanisms (Alberini 2005), as well as to play a similar role: making the memory trace solid and long-lasting (Nader and Hardt 2009).

There is evidence for the reconsolidation phenomenon in different species (Nader and Hardt 2009; Schiller and Phelps 2011) and for different types of memory (Alberini 2005; Nader and Hardt 2009; Besnard, Caboche et al. 2012; Dudai 2012). The typical design for examining the reconsolidation phenomenon is a three-day experiment. On the first day of experiment, encoding or learning of the material takes place. On day two, the consolidated memory is

reactivated and interfered with, in order to show the disruption of the original memory traces, and on the last day, reconsolidation is measured through enhancement (Rodriguez, Horne et al. 1999), impairment (Nader, Schafe et al. 2000a) or updating with new information (Lee 2008b).

In the reconsolidation literature, there are two hypotheses regarding that question of what happens with the memories once reactivated during the reconsolidation process (see Alberini (2011, for a review). First hypothesis proposes that memory is updated via the integration of new information into the destabilized original memory (Sara 2000b; Dudai 2004); the second suggests that original memory is changed not only in content, but also in strength (Sara 2000a). In support of the integration hypothesis, several neuroimaging studies identified a link between sleep spindles activity and the integration of new memories into previous knowledge (Tamminen, Payne et al. 2010; Fogel and Smith 2011). In support for the second hypothesis, Lee and colleagues showed stronger contextual fear memories after second learning session (Lee 2008a). Subsequent studies demonstrated that lateral prefrontal cortex (PFC) may play a role in the memory strengthening process, as evidenced by studies using repetitive transcranial magnetic stimulation (rTMS) (Sandrini, Censor et al. 2013). Specifically, Sandrini et al. (2013) stimulated the right lateral PFC region by rTMS, 10 minutes after the memories were reactivated by spatial-contextual reminder. They observed the strengthening of verbal episodic memories in the stimulation group the next day as compared to the two other control groups; one without reactivation and the other in which the vertex instead of PFC was stimulated.

In humans, first reconsolidation studies investigated this phenomenon for non-declarative memory, specifically for procedural memory using motor finger tapping task (Walker, Brakefield et al. 2003). The speed and the accuracy of task performance were compared in eight groups of participants who trained for either one or two motor sequences,

immediately or with an interval of six hours between them, and they were tested either in the same day as that of the training, or the next day. The authors reported lower performance for the groups that had the memory trace reactivated (using reminder cues) before learning a new sequence. In the same study, the reconsolidation was found to be time-dependent given that the authors could not find any decrease in performances for the groups that were tested just after being interfered with the new motor sequence to be learned (Walker, Brakefield et al. 2003).

Recently, the reconsolidation was studied using declarative memories. Forcato and Hupbach were the first to investigate the reconsolidation process in the human episodic memory (Forcato, Burgos et al. 2007; Hupbach, Gomez et al. 2007a). In Forcato's 2007 study, the authors used sets of distinct verbal materials to be learned over two sessions with an interval of a day in between. The specific context of learning environment plus a cue syllable of the verbal material were used as a reminder that was given either just before the second training or with a longer interval. On day three learning was tested for both sets of materials, but in different orders for different groups to check the effect of interference in learning. Authors measured the reconsolidation as retrieval-induced forgetting, where remembering a material causes the disruption of retrieval of related materials from memory, a concept initially introduced by Anderson (Anderson, Bjork et al. 1994). Forcato showed the reconsolidation effect in declarative memory in a time window of 5 min or 6 h after a memory reactivation (Forcato, Burgos et al. 2007), thus providing evidence that reconsolidation process is time-dependent. In a similar study, Hupbach and colleagues examined reconsolidation in episodic memory, also using a three-day experiment design. Participants were divided in three groups based on whether they had a reactivation session or not, and whether they were tested immediately after second session or not. During the initial learning session participants learned a list of 20 objects; these

were shown to subjects and then were placed in a blue basket. On second day of experiment, experimenters used the same blue basket (empty) as a reminder in the reactivation groups, prior to learning a new list of objects. They found no differences between groups in terms of the number of correctly recalled objects, but they could show intrusions from the second list of objects in the recall of first learning (Hupbach, Gomez et al. 2007a).

1.2.5 – Retrieval

Retrieval is the process in brain in which the stored memory traces become accessible and available for use (Sara 2000b; Nader 2003). One of the key factors that can influence the retrieval process and memory performance is the use of retrieval cues. It has been well established that free recall of the learned material is more difficult than that aided by cues (Thomson and Tulving 1970; Roediger III 1973). The cues used in retrieval range from internal cues, such as the psychological states and moods, to external ones, such as the environmental conditions (smell, sounds, color, etc.). Retrieval cues could be either dominant or weak depending on their degree of similarity to the cues that were present during the encoding phase. In fact, there is ample evidence that the effectiveness of retrieval depends on the similarity between the encoding and retrieval context (Tulving and Osler 1968; Lockhart and Craik 1990; Brown 1991), a principle that has been called "encoding specificity" and has been conceptualized by Tulving and Thomson (Tulving and Thomson 1973).

Retrieval is typically assessed through two types of memory tests: recall and recognition. Given that there are fewer cues used in recall tasks/tests, the recall is always more difficult and the performance is usually poorer than that of recognition. It is generally understood that well-

encoded information will be both recognized and recalled, whereas the weakly encoded information may just be recognized, but not recalled (Tversky 1973).

Several imaging studies using fMRI have shown increased medial temporal lobe (MTL) activity during recall memory tasks; however it is difficult to distinguish or to identify the precise memory process associated with this activation (i.e. encoding vs. retrieval), given that there could have been incidental encoding during retrieval. (Buckner and Wheeler 2001; Stark and Okado 2003) . A network of cortical regions, other than MTL was also reported to be involved during a successful retrieval, including the posterior cingulate, posterior parietal, and prefrontal cortex (PFC) (Konishi, Wheeler et al. 2000; Rugg and Henson 2002; Kim 2013; Nelson, McDermott et al. 2013). The PFC, a region of default mode network, was generally linked to retrieval of declarative memories (Lepage, Ghaffar et al. 2000). More specifically, different part of the PFC were activated as a function of different memory tasks (Cabeza, Locantore et al. 2003). For example, it has been shown that left PFC was activated for retrieval of pictures and words (Spaniol, Davidson et al. 2009).

1.2.5.1– Recall

The recall is the process by which the information is actively retrieved from long-term memory, either in the absence or presence of external cues. The recall is based on more complex brain processes that would facilitate the retrieval of the information from memory (Postman 1963).

There are three types of recall: free, cued, and serial recall. Free recall is seen when the learned material is reproduced freely, in the absence of specific external cues, in any order. For example, subjects are given a list of words to remember and then are requested to recall as many

of them, in any order. Cued recall describes the situation in which the recall is aided by providing some cues or hints. One example of cued recall would be an associative memory task in which participants have to learn pairs of elements and – at recall – they are presented with one of the pair element while being asked to recall the other. Finally, serial recall is operationalized by tasks in which subjects are asked to remember not only the items, but also their order, since they are asked to recall them in the order in which they were originally presented.

Imaging studies have shown frontal lobe activity, mostly in prefrontal cortex that is associated with recall performance. For instance, Gais and colleagues used a list of 90 semantically related word pairs to be learned by two groups of participants in sleep and sleep-deprived conditions. They examined the memory recall before and 48 hours after learning. Both sessions of learning and recall took place inside the MRI scanner. Results showed the enhancement in memory in the sleep group compared with the awake group. The imaging results showed the activation of similar brain regions during learning and retrieval. In the post-session after sleep deprivation, activation of hippocampus was coupled with left precuneus whereas, in sleep condition, the authors reported a strong correlation between hippocampus and the ventral mPFC, hence indicating the interaction between hippocampus and neocortex, a sign of the transferring stage from hippocampus to the cortex (Gais, Albouy et al. 2007).

1.2.5.2– Recognition

Recognition is a memory testing procedure that assesses the cognitive process of matching the information found in a stimulus with that from previously encoded memories. Compared to recall, it can occur more quickly, as demonstrated by the superiority of recognition over recall tests and by the fact that less information is needed for a successful recognition, than

recall (Postman 1963). Recognition could be used to assess memory for both verbal materials such as words or for visual elements, like faces.

Regardless of the material, two kinds of recognition tests are commonly used: yes/no recognition, and forced choice recognition memory test. In the typical yes/no test, subjects are presented with single items, drawn from a mixture of previously learned items (old items) and new ones, while being asked to respond yes or no to indicate whether the current item was previously learned or presented or not. It is thought that participants make this choice by relying on the familiarity of the stimulus. In a forced choice recognition test, subjects are presented with pairs of items (one new and one old) and are being asked to indicate which item of the pair was presented earlier.

Recognition requires only one simple familiarity decision. Two types of information influence this decision: item and context information. Item information includes the properties of the item to-be-remembered, such as the meaning or phonological aspect of a word, or the visual content of a photo. Context information include the environmental characteristics, the temporal states and internal subject variables like mood (Malmberg and Shiffrin 2005). There are some other factors, which affect the recognition performance, such as the number of studied items during the encoding phase; as the number of items to be learned increases, the recognition accuracy decreases, based on item noise model (Criss & McClelland, 2006).

There are four types of outcomes in a classical yes/no recognition memory test based on the subject respond and the types of items. If a subject correctly recognised the old items, that is considered as a hit. If the old items are not accurately recognised, then that constitutes a miss. For a new item, if the subject mistakenly recognizes it as old, the answer is counted as a false

alarm, whereas if the item is correctly recognized as new, it is then considered as a correct rejection. Hit or false alarm rates alone are not good discrimination indicators for recognition performance. However, based on Signal Detection Theory (Green and Swets 1966; McMilan and Creelman 2005), combining or using both the hit and false alarm ratios can provide a better measurement for memory performance in yes/no recognition tasks: the discriminability or d-prime, and bias or C. The d-prime index reflects the true ability of the subject to discriminate between the new and old items. The greater the d-prime, the better the discriminative performance. The C value indicates the conservative or liberal bias (i.e. subjects are more likely to respond 'no' vs. 'yes', respectively), based on whether C has negative or positive values, respectively.

1.2.6– Forgetting

Failure to retrieve information by either recall or recognition is defined as forgetting. Ebbinghaus was the first to systematically investigate this phenomenon and to show that most of the forgetting happens in the first hours after learning (Ebbinghaus 1885). He was also the first to describe the rate of forgetting (i.e. the forgetting curve) for the memorization of lists of nonsense-word pairs.

Two theories have been proposed to describe and explain the forgetting phenomenon based on the longevity of the stored information. The first, the decay theory, proposed by Brown in 1958 states that any mnemonic process is accompanied by rapid forgetting or automatic fading of the learned information. Brown proposed this theory by positing that the memory traces will decay after a short delay and that the forgetting is time-dependent (Brown 1958). In his study, he prevented the rehearsal of the learnt verbal materials by presenting digits to be read

aloud during the retention interval (Brown 1958). Subjects were asked to read out two sets of stimuli during presentation. First set consisted of pairs of consonants while the second, additional set, consisted of five pairs of number digits. In the experimental group, subjects were asked to remember the first sets of stimuli while reading out the additional set items. Comparing to that, in the control group there was no additional set to be read out by subjects and the interval before recall was remained unfilled. Researchers showed a better recall performance in the control group as compared with the experimental group, thus demonstrating the immediate decay forgetting. As mentioned, the decay theory seems to explain better the short-term rather than long-term memory loss; the latter type is hard to be tested, given that it is impossible to have a very long 'empty' time interval between learning and recall. The second theory about forgetting, the interference theory, proposes that older memory traces are disrupted by other, newer, memory traces (MacGeoch 1942; Underwood 1957) via interference, and that the degree of forgetting depends on the similarity of these two competing memory traces. This interference process may cause forgetting in two ways: proactive, meaning that the previously learned items disrupt or interfere with the later-acquired memory, or retroactive, which occurs when the old memories are changed or affected by subsequent learning.

In recent years, there is research to suggest that forgetting may actually play a functional role in memory. For instance, in a review article, Hardt et al. (2013) presented a model of active forgetting as a memory decay process that is essential for the proper functioning of the brain. In support of this idea, the authors mentioned that the decay phenomena seems to occur during sleep, whereas the interference phenomena seems to be specific to wakefulness, in the active phases of memorizing, such as encoding and retrieval. The authors provide evidence from the animal literature investigating the similarity of the neuronal firing patterns of different brain

systems. For example, the hippocampus is considered to be a brain area with efficient pattern separation; as such, the interference effect is reduced, as well as the overlap between learned materials. In contrast, however, this area is susceptible to forgetting by decay. Other parts of the brain are more resistant to decay because they have minimal sensory integration and less pattern separation, but they will be more susceptible to interference (Hardt, Nader et al. 2013). This model of active forgetting seems to be consistent with the hypothesis that there is ongoing neurogenesis in the hippocampus, which leads to a gradual decay of memories that are dependent on this structure (Frankland, Köhler et al. 2013).

A recent study on this topic, showed that the primary cause of forgetting may be found in the process by which memories are retrieved, specifically; whether the retrieval is based on active recollection, or it is based on familiarity (i.e. having the sense of it being already lived or experienced) (Sadeh, Ozubko et al. 2014). To further demonstrate this point, in a later study, Sadeh et al. used confidence rating to test the effect of forgetting on the low and high-confidence memories and they showed that high-confidence memories, as well as the recollection-based memories were more prone to decay than to interference, in contrast with the low-confidence memories and the ones dependent on familiarity, which were more prone to interference than to decay (Sadeh, Ozubko et al. 2016). Whatever its cause, forgetting does not necessarily mean that the memory traces are actually lost, but also that they may be just inaccessible at the time of remembering. That is why sometimes it is easier to recover memories by using reminders or cues (Tulving 1974). Despite much research on forgetting, there is still no unified view regarding its causes (Wixted 2004).

Chapter 2 – Objective and Hypotheses

Objective

The principal objective of this study is to provide direct evidence of the effect of interference on reactivation at the behavioral level in young healthy subjects for the current model of memory reconsolidation based on the reactivation of memory traces. This aim was reached using a 3-day experimental interference paradigm and an innovative combination of recall and recognition memory tests that allow for the assessment of the memory strength of individual memory traces ranging on a continuum from the forgotten to the reconsolidated.

Paradigm

The experimental paradigm relied on a visual object spatial memory task in which two group of participants had to learn the spatial location of 36 images inside a 6*6 matrix. After following the same procedures for the memory encoding on the first day and testing of the memory consolidation on the second day via a cued-recall test, one group was exposed to an interference task (i.e. learning a second matrix consisting of the same items placed in different locations). In the last experimental session on the third day, both groups were tested for the reconsolidation of the initial matrix using cued-recall and recognition tests.

Hypotheses

We expect that subjects in interference group will have a significant decrease in the memory performance on day three for both recall and recognition test compared to the control group (non-interference). We expect that this decrease will be higher for consolidated memory traces as compared to the non-consolidated ones. Finally, we expect to observe differences

between groups (interference vs. non-interference) on the third day for memory traces of different memory strength suggesting that the reconsolidation is qualitatively different than the consolidation process.

Chapter 3 – Methods

3.1 - Participants

A group of 40 healthy young right-handed adults aged between 20 and 35 years of age (mean, SD 24.75 ± 3.69; 16 males) participated in our study. Exclusion criteria were assessed via an online survey and included the presence or a history of any neurological or psychological disorders or of insomnia. Having a good sleep quality was an important inclusion criterion. Participants' eligibility assessment via the survey included the Pittsburgh Sleep Quality Index (PSQI), which assessed the sleep quality over the past month (Buysse, Reynolds et al. 1989), as well as the Beck Depression and Beck Anxiety (Beck 1973; Steer and Beck 1997) inventories. During the entire study, participants' sleepiness was assessed using the Stanford Sleepiness Scale in each of the three days of the experiment (Hoddes, Zarcone et al. 1973).

3.2 - Procedure

The study was approved by the Ethics Committee of the Research Center of the Montreal Geriatric Institute affiliated with the University of Montreal. Participants signed a consent form and were financially compensated for their participation in the study.

The study took place over three consecutive days with a 24-hr interval between each of the three experimental sessions. Participants were randomly assigned to either an Interference or Non-Interference group.

On the first day (Day 1), all participants were required to learn (encode) the spatial location of 36 images within a 6*6 matrix that they could see while sitting at a comfortable distance from a computer screen (Matrix A). Participants were first explained the task and

shown a demo of it. Following the successful completion of the demo phase (i.e. familiarization with the task), the learning phase commenced. Participants alternated between presentation blocks during which they were shown the location of each of the 36 items within the 6*6 matrix (one item at a time), and test blocks during which they had to indicate the correct location once the item was presented just above the matrix (cued recall condition). The learning phase consisting of the presentation and test phases lasted until participants reached a success rate criterion of 70 percent. After 10 minutes, the learning phase was followed by an immediate recall phase, during which the subjects' level of encoding of Matrix A was assessed. On Day 2, all participants performed a 24 hour cued-recall test of Matrix A at about the same time of day as during the learning phase, and then completed the Stanford Sleepiness Scale. Following this short testing session, participants in the Non-Interference Group were sent home, whereas those in the Interference group were required to acquire a second matrix (Matrix B) consisting of the same 36 items, but presented in different locations than in the Matrix A. The learning phase for Matrix B followed the same procedure as that for Matrix A, and ended again when participants in the Interference group reached a success rate criterion of 70 percent. This second learning phase was followed by an immediate recall of Matrix B 10 minutes after in order to assess the subject's level of encoding of this second matrix. On the third day (Day 3), all participants were asked to perform a cued-recall test of Matrix A, and completed again the Stanford Sleepiness Scale. Participants in the Interference Group performed a cued-recall test of Matrix B, whereas those in the Non-Interference Group waited for 5 minutes. After the recall tests, all participants performed a recognition test for Matrix A. This test consisted of 72 trials during which the 36 images used previously were presented twice; once at the same location as in Matrix A, and the second time at a different, randomly assigned location, the order of presentation in the Matrix

A or random location being counterbalanced. In each trial participants had to indicate whether the item location was the same as that of Matrix A or not.

3.3 - Task

We used a visuospatial learning task that was adapted from Sonni et al. (2015), but with a higher difficulty given that we increased the matrix size from 5*4 to 6*6 locations. Participants' task was to memorize the spatial location, within the 6*6 matrix, of 36 images depicting everyday life objects belonging to four different categories: animals, vehicles, clothes, and fruits (Figure 3.1).

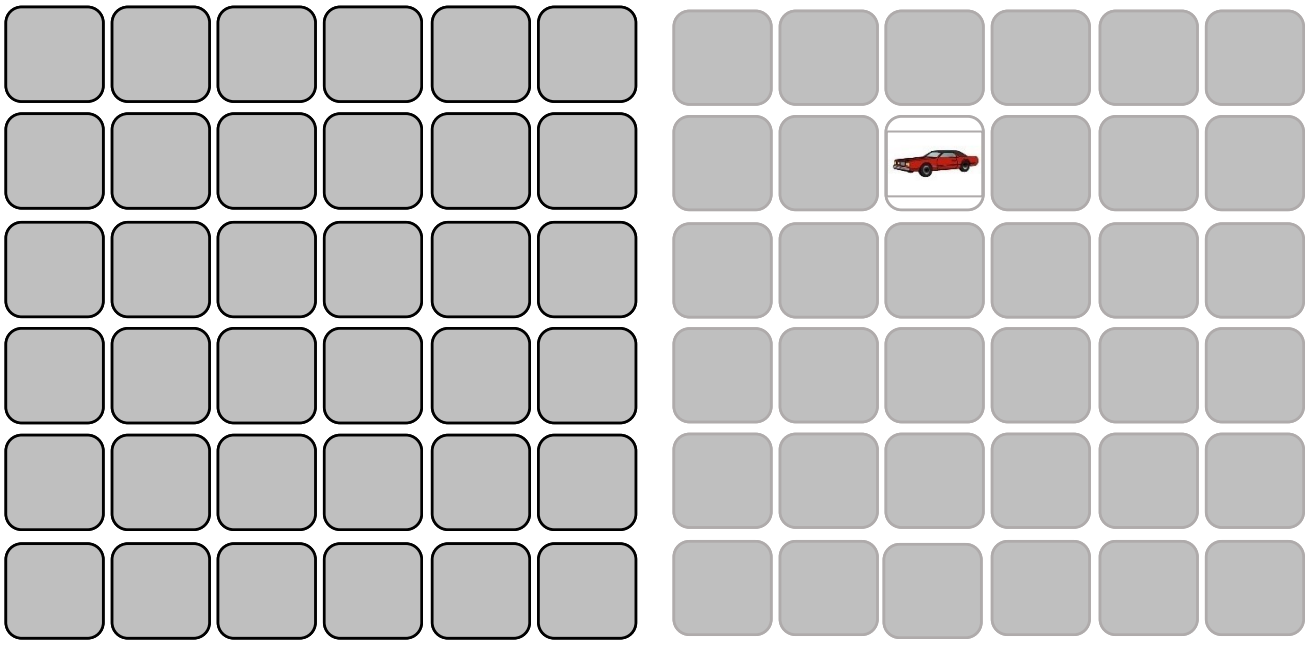

Figure 3.1. The matrix used in our study in blank (left), and during presentation phase (right).

The task had a demo phase in which three geometrical shapes circle, triangle, and rectangle) were presented at different locations. This phase had the dual purpose of familiarizing the participants with the task, but also served to exclude participants who were unable to

memorize the location of the geometrical shapes in two consecutive demo blocks. Yet, it should be noted that we did not exclude any participant based on their performance in the demo phase.

The learning phase consisted of pairs of alternating presentation and test blocks, all in this order. During the presentation blocks, each of the 36 images was shown, one at a time, at its location for three seconds. In the test blocks, the matrix would be blank and each image was presented on top of the matrix for 2 seconds, followed by 5 seconds during which participants had to indicate its location by clicking with the mouse within the appropriate location (box) within the matrix. Feedback was provided to participants only during the learning phase and only at the end of each test blocks in a form of a numerical score (e.g. 18 out of 36) indicating their overall recall performance. Participants had to obtain a minimum performance score of 70% (25 out of 36 correctly recalled locations) in order to complete the learning phase. Importantly, only one participant was unable to reach this criterion after 10 blocks of presentation, and the latter subject was thus excluded from our study.

We used the same 36 images, but two sets of locations in our study. The first set of location (Matrix A) was learned by all participants, whereas the second set (Matrix B) was learned only by the participants in the Interference Group, as described in the procedures. Memory performance for Matrix A and B was tested via cued-recall tests, which consisted of a single test block, identical to the ones during learning phase, but with no feedback regarding the participant's performance. In addition, on the third day, a recognition test for Matrix A was performed by both groups, as indicated in the procedure above.

3.4 – Dependent variables

The proportion of items correctly recalled during the cued-recall tests of either Matrix A or B, the proportion of items correctly or incorrectly recognized from Matrix A (hit and miss ratio, respectively), as well as the proportion of items correctly or incorrectly recognized as not being from Matrix A (correct rejection and false alarm ratio, respectively) constituted the main dependent variables. The groups (Interference vs. Non-Interference) and the testing days (Day 2 vs. Day 3) constituted the independent variables. Consolidation of Matrix A was operationalized as the proportion of items correctly recalled during both the immediate recall test after learning (Day 1), as well as during the recall test on Day 2.

For the recognition test, given that each item was presented twice (once in the original location from Matrix A, once in a different location), there are four possible outcomes: a true positive (TP - hit) or a false negative (FN – miss), when items were presented in the original location, and a false positive (FP – false alarm) or a true negative (TN – correct rejection), when items were presented in a different location. We considered various combinations of these outcomes at the recognition test to reflect the strength of the memory trace, presented here in the order of increasing strength: FN + FP, TN + FN, TP + FP, TP + TN. Given that on the Day 3 participants had to perform both a cued-recall and recognition tests, we decided to use the above mentioned outcomes from the recognition test and the outcome from the recall test (recalled vs. not recalled) to classify all items in one of the 8 categories on a custom-made memory strength continuum ranging from forgotten to complete reconsolidation (Figure 3.2). Specifically, forgotten memory traces were for items that were not recalled and were (FN + FP) at the recognition test. These items were below the recognition and recall thresholds. Next

categories on the memory strength continuum included items that were recognized, either partially or completely, and also correctly recalled (i.e. above the recognition threshold, but bellow the recall threshold), as well as items that were not recognized despite of being recalled (probably by chance). We considered all these items to be labile memory traces. Next on the continuum were items that were recalled, but partially recognized; these items were considered to be partially reconsolidated. Finally, items that were both recalled and completely recognized (TN+TP) were considered to reflect completely reconsolidated memory traces (Figure 3.2).

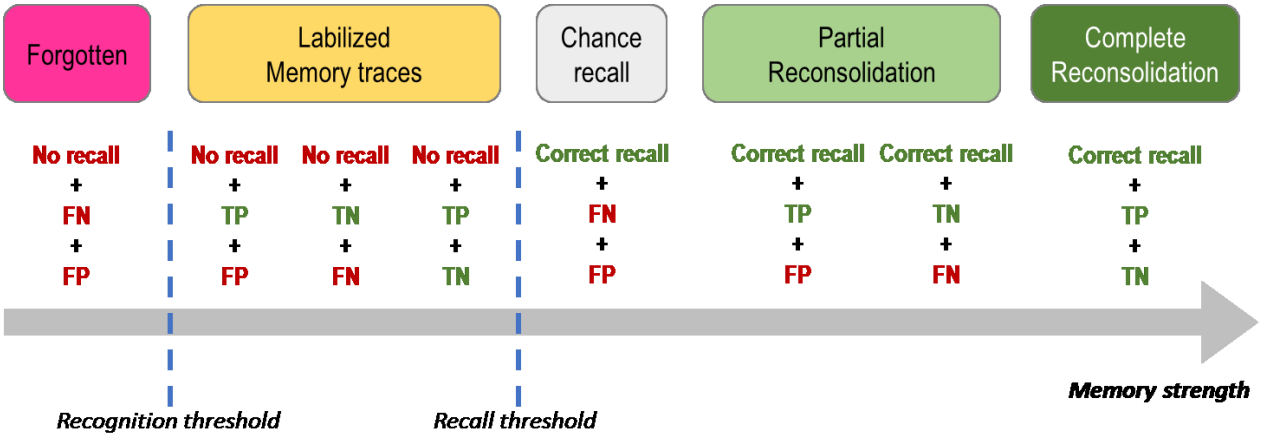

Figure 3.2. The memory strength continuum based on the performance at the cued-recall and recognition tests on Day 3 for items that were consolidated after the first two days. FN (miss rate), FP (false alarm), TP (hit rate), TN (correct rejection).

To our knowledge, this classifications of items based on memory strength has never been implemented as such in the memory reconsolidation literature. Whereas there are some studies investigating the phenomenon of recognition failure of recallable items (i.e. items that could be recalled, but not recognized (Tulving and Osler 1968; Watkins and Tulving 1975), no study in the reconsolidation literature has investigated the phenomenon of partial vs. complete reconsolidation of memory traces. However, for the purpose of analyses, we considered that the items that were recalled but not recognized were items that were recalled by chance.

3.5 – Statistical Analysis

We used mixed repeated-measures ANOVA to assess the interaction between independent variables (Group*Day) indicating the effects of interference on different dependent variables describing the memory performance. Pairwise comparisons between different conditions in the ANOVA were performed using the Bonferroni correction to account for multiple comparisons. Group differences were assessed using independent samples t-tests. In all analyses we used the statistical threshold of $p<0.05$.

3.6 – Methodological Approach

Both consolidation and reconsolidation process in declarative memory tasks can be assessed by using verbal or visual materials. We decided to use a visuospatial learning task adapted from Born et al. group (Rasch, Büchel et al. 2007a). The advantage of this type of task is that it is not language-dependent and its level of difficulty can be easily matched across groups and conditions. In addition, given the multicultural nature of Montreal community and the diversity of the languages spoken, we preferred to use a task that is non-verbal.

This type of task could be given either in an associative format, such as having to remember the spatial locations of pairs of objects similar to (Rasch, Büchel et al. 2007a) study, or by presenting the spatial locations of each item individually (Sonni and Spencer 2015). The original task proposed by Born et al (Rasch, Büchel et al. 2007a) consisted of 15 pairs of cards representing photos of simple daily life objects on a matrix of 6 by 5. Usually, in the associative format of this task, it is not easy to determine which element of a given pair was better encoded; and thus it is difficult to decide which element of the pair should be used as the reactivation or retrieval cues, as it could be affected by its initial encoding. In addition, in the associative format,

one cannot easily use free recall as a memory test. For all these reasons, we preferred to use a single element presentation approach in our study. Another advantage of using the present format is that there is more distinctive items (36) that subjects need to recall, and thus that it would be easier to have behavioral differences between consolidated items and non-consolidated memories. In light of these issues, we selected our task based on Sonni et al. study (Sonni and Spencer 2015).

In our study, participants were instructed to remember the location of 36 images depicting 4 categories (clothing articles, animals, vehicles, tools) inside of a 6*6 square matrix (Figure 3). Encoding took place during the presentation phase, during which each image was presented for three seconds and participants had to try to remember their location within the matrix (Matrix A). After all elements were presented, a brief cued-recall test followed. This time, each image was presented on top of the matrix for two seconds and participants had to click with the mouse the location where this element was placed during the presentation phase. The feedback was only presented at the end of the cued-recall test in terms of the number of images correctly recalled in the right location.

Once the participants reached the learning criterion, an immediate cued recall test was performed without giving any feedback at the end, to assess the immediate learning. Next day after learning of Matrix A, all participants performed a cued-recall test without feedback, to assess memory consolidation. Then, an interference task using the same stimuli, but placed in different locations as compared to the original matrix (matrix B) was administered only to the interference group (half the participants). The encoding of Matrix B followed the same procedure as that for Matrix A. On the last day of experiment, cued recall tests were performed

for Matrix A (both groups) and Matrix B (only the interference group), followed by a recognition test for elements from Matrix A.

There are some key differences between our task and the versions used previously in the literature. These differences are presented in the next sub-sections.

3.6.1 - Feedback

There are two types of feedbacks that are usually used during learning: immediate and delayed. Immediate feedback provides the subject with the knowledge of correct or wrong answer immediately after each trial (Rasch, Büchel et al. 2007a), whereas delayed feedback provides the knowledge of the overall performance, such as the percentage of the corrects answers, usually later, after a set of trials. Previous studies demonstrated that immediate feedback facilitates learning by decreasing the amount of false memories present at the recognition test (Jou and Foreman 2007; Mcconnell and Hunt 2007). In our task, we have provided participants with only general feedback, at the end of each block of 36 trials during the learning (i.e. memory encoding) phase, without indicating which specific items were incorrectly recalled or misplaced. This approach has the advantage of not affecting the participants' encoding strategy or the performance at the subsequent recognition test on the last day of the study.

3.6.2 – Consolidation Measurement

In previous studies, such as that by Rasch and colleagues (2007), the percentage of correct answers during the delayed cued recall test relative to participants' performance at the last learning trial was considered as a measure of consolidation (Rasch, Büchel et al. 2007a). However, this approach does not ensure that this consolidation measure included exclusively

items that were both encoded (i.e. present during the last learning session), as well as recalled during the delayed recall test. To address this issue, in our study, we used the proportion of item correctly recalled both at the immediate (Day 1), as well as at the delayed recall test (Day 2), as our measure of consolidation. The advantage of our approach as compared to that of Rasch et al. (Rasch, Büchel et al. 2007a), is that it allowed us to analyze the effect of interference on consolidation as well as non-consolidated items. The recall and recognition tests on Day 3 served to provide evidence for the processes of reactivation and reconsolidation, something that was lacking in previous studies.

3.6.3 – Strength of Memories

Previous studies did not consider or assessed the memory strength for various encoded items. In fact, to our knowledge, there is no memory reconsolidation study which has used interference paradigms and has operationalized and/or investigated the memory strength for individual items along a continuum, from completely forgotten items to the ones that are partially and completely reconsolidated. In the current study, we used participants' performance at the recall and recognition memory tests undertaken in the last day of the study to characterize the memory strength for the items which were correctly recalled immediately after learning (Day 1) and after a night of sleep (Day 2). Based on the combination of participants' performance at the two types of tests, we can assign individual items along the memory strength continuum as presented in Figure 3.1.

3.6.4 – Complete Forgetting

Kintsch introduced a two-process model of recall in which the items must be both recalled and recognized in order to be successfully retrieved (Kintsch 1970). By considering

only the consolidated items in our analysis and classifying them along the above-mentioned continuum (Figure 3.1), we were able to differentiate between items that are recalled by chance (i.e. recalled but not recognized) and those that are completely forgotten (neither recalled, nor recognized), something which has not been considered in the previous studies. This is a significant innovation in the memory reconsolidation research given that we will be able to assess whether the reconsolidation process is qualitatively the same or different than the consolidation per se. To this end, we expect that the distribution of consolidated items along the memory strength continuum will be different between the interference and non-interference groups, in line with the idea that reconsolidation is a qualitatively different process than consolidation.

3.6.5 – Task Design

In order to minimize the effect of using specific rules or meta-strategies (i.e. mnemonics) during memorization (i.e. associating item categories with specific matrix locations), we employed a custom-made algorithm that had specific placement rules when designing the matrix (self-developed software of our laboratory at Unite de Neuroimagerie Fonctionnelle (UNF) in 2017). Specifically, of the thirty-six images which were derived from four different categories, we placed one item from each category at each corner of the matrix, we sought not to have two items from the same category next to each other and we randomized the item location from participant to participant in order to avoid pairing of an item with a specific location across subjects.

Chapter 4 – Results

The purpose of the current study was to examine the consolidation and reconsolidation processes in declarative memory for visuospatial information by using an interference paradigm and an experimental design that favor a novel approach on data analysis at the item level. Unlike previous studies investigating these mnemonic processes with the same type of material (Forcato, Burgos et al. 2007; Hupbach, Gomez et al. 2007a), our experimental design allows for the assessment of performance separately for each mnemonic process (i.e. learning, consolidation, reconsolidation, reactivation etc.) and of the effects of interference on these processes. In addition, to our knowledge, this is the first study to investigate the interference effect on consolidated and non-consolidated items in a declarative spatial memory task.

4.1 – Descriptive Statistics

Descriptive statistics provided in Table 1 include mean scores and standard deviations for the subjects' baseline performance (performance in the last presentation/cued recall test at the end of encoding/learning phase), as well as the number of loops (alternating between the presentation and cued-recall of the matrix) to reach criterion at encoding for both matrix A and matrix B.

Socio-demographic variables including age, gender, level of education as well as the scores of Pittsburgh Sleep Quality Index and Stanford Sleepiness Scale did not show any significant differences between two groups (Table 2).

	Interference	Non-interference
Matrix A cued-recall at last learning loop	29.5 ± 2.61	28.75 ± 2.55
Matrix B cued-recall at last learning loop	29.8 ± 2.31	-
Matrix A immediate recall (Day 1) *	29.45 ± 2.91	26.65 ± 3.08
Matrix B immediate recall (Day 2)	28.55 ± 3.38	
Matrix A delayed recall (Day 2)*	27.2 ± 3.78	23 ± 5.14
Number of loops (matrix A)	3.7 ± 1.03	4.1 ± 1.37
Number of loops (Matrix B)	3.3 ± 1.08	-

Table 1. Number of matrix elements recalled (out of 36) and the number of learning loops for both matrix A and B and standard deviation in interference and non-interference group. * $p<0.05$

	Interference (N=20)	Non-interference (N=20)	Mean difference	Sig. (2-tailed)
Age (years)	24.95 ± 4.03	24.55 ± 3.43	-0.4	0.73
Sex (F:M)	14:6	12:8		0.52
Education (Years)	15.75 ± 4.68	16.05 ± 4.68	0.3	0.83
Stanford Sleepiness Scale Score	1.39 ± 0.69	1.87 ± 0.88	0.48	0.08
PSQI	2.55 ± 1.05	2.15 ± 1.56	-0.40	0.34

Table 2. Comparison of demographic variables such as age, gender and education plus the Pittsburgh Sleep Quality Index and Stanford Sleepiness Scale scores between Interference and non-Interference group (mean ± standard deviation).

4.2 – Overall Memory Performance

Both groups had similar performance on the cued-recall test during the last loop of training on Day 1 (Table 1). However, the performance of memory in the immediate recall on Day 1 and delayed recall on Day 2 was significantly higher in the Interference than in the Non-interference group (Table 1).

The effect of the interference task was significant both when considering group differences in performance during the recall (Figure 4.1), as well as during the recognition memory tests (Figure 4.2).

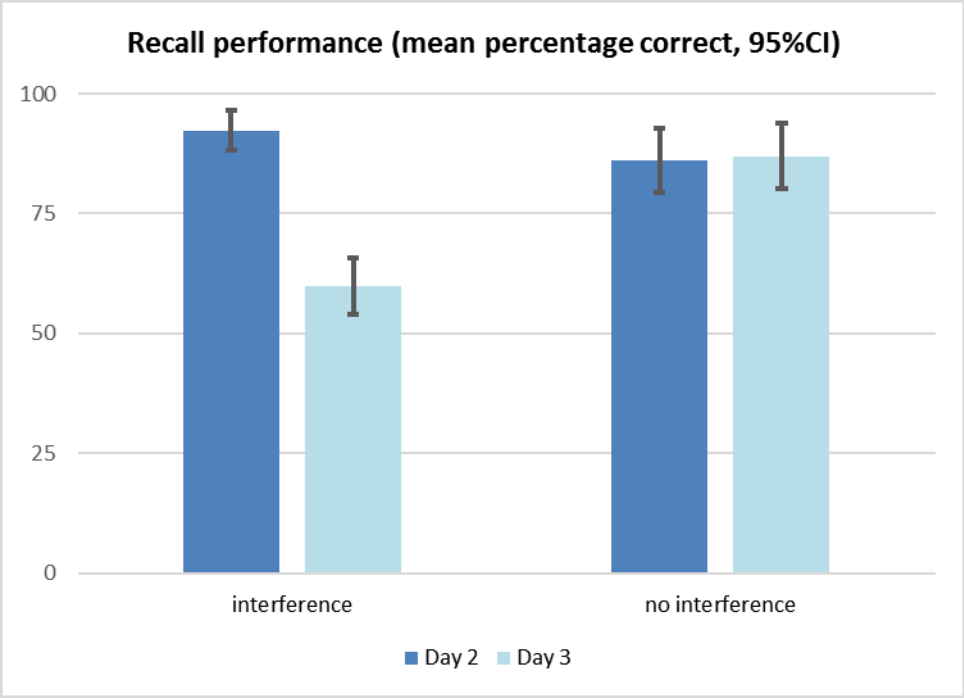

Figure 4.1. Recall performance on D2 and D3 expressed as percentage of immediate recall (D1).

Regarding the recall performance, there was a significant day*group interaction effect ($F_{1,38}$=74.7, $p<0.001$) indicating that the performance of the Interference Group was

significantly lower on Day 3, both when compared with that of the Non-Interference Group, as well as with their own performance on Day 2.

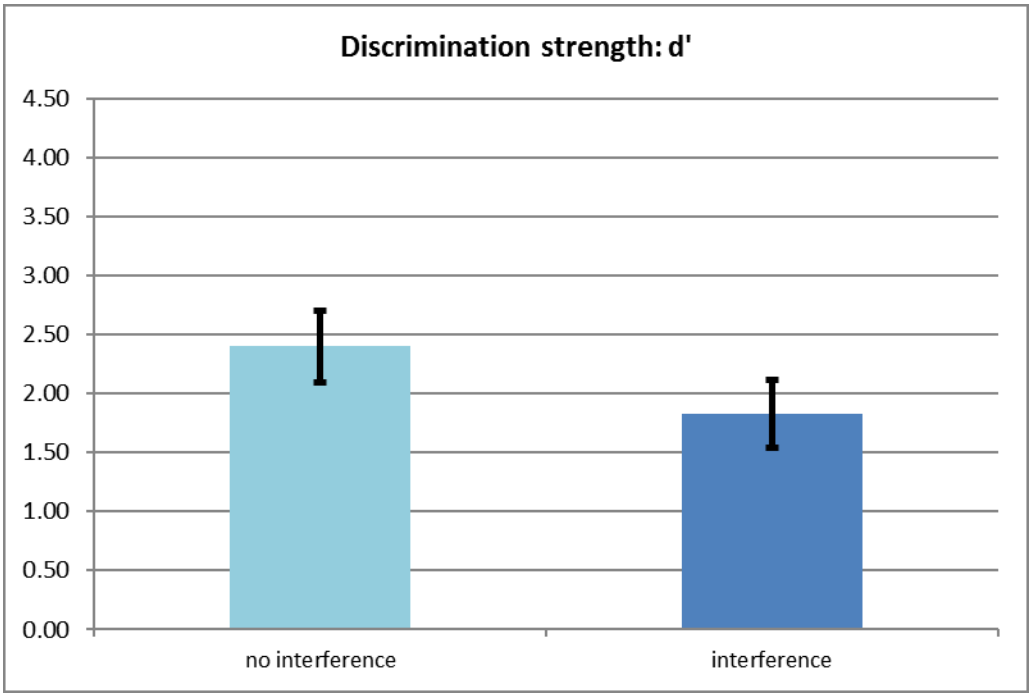

Figure 4.2. Memory sensitivity for discrimination of items were measured by d-prime accounting both hit rate and false alarm scores of recognition test for interference and non-interference group.

With regards to the overall recognition performance, as assessed by the d-prime parameter (thought to reflect the memory strength), we observed a significant difference between the two groups (t_{38}=2.76. $p<0.01$) indicating that the strength of memory in discrimination between old and new items was significantly weaker in the Interference than in the Non-Interference group.

4.3 – Memory Consolidation and Interference Effect

Comparing the matrix elements which were correctly recalled across the first two versus three days we have found a significant day*group interaction effect ($F_{1,38}$=72.55, p<0.001) as seen in Figure 4.3.

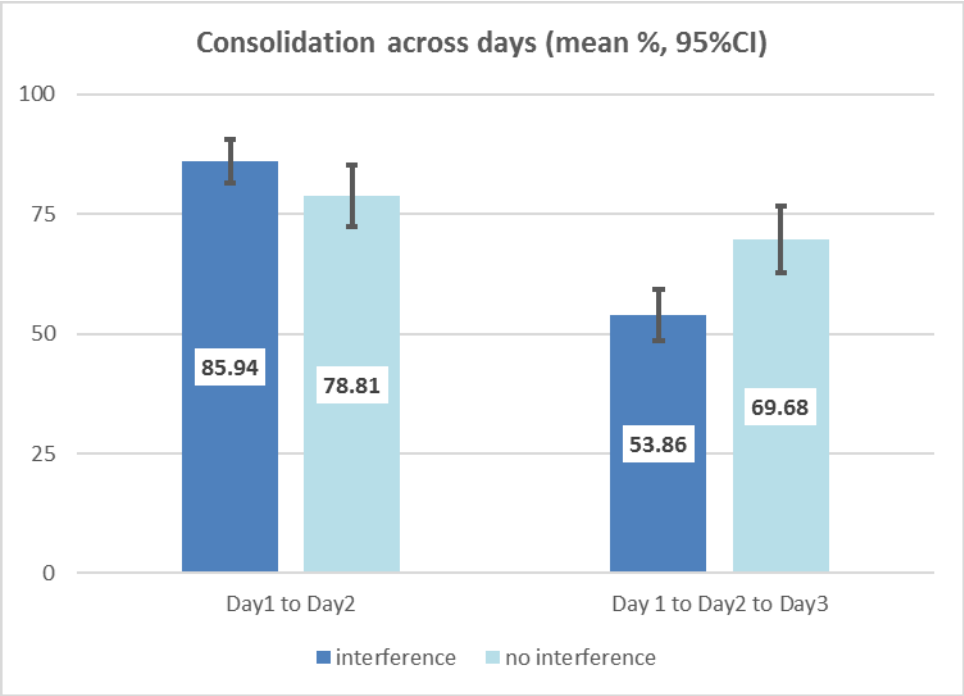

Figure 4.3. The effect of interference on consolidated items through the first two days vs. all three days by measuring recall performance.

The interaction effect indicates that, while there is no significant difference between the two groups when comparing the percentage of elements consolidated over the first two days, there is a significant group difference when comparing the elements consolidated over all three days, reflecting a deleterious effect of the interference for the items that were consolidated after learning and a night of sleep.

The effect of interference on consolidated elements is also seen when comparing the recognition performance of the two groups for elements consolidated over 2 or 3 days, as seen in Figures 4.4 and 4.5, respectively.

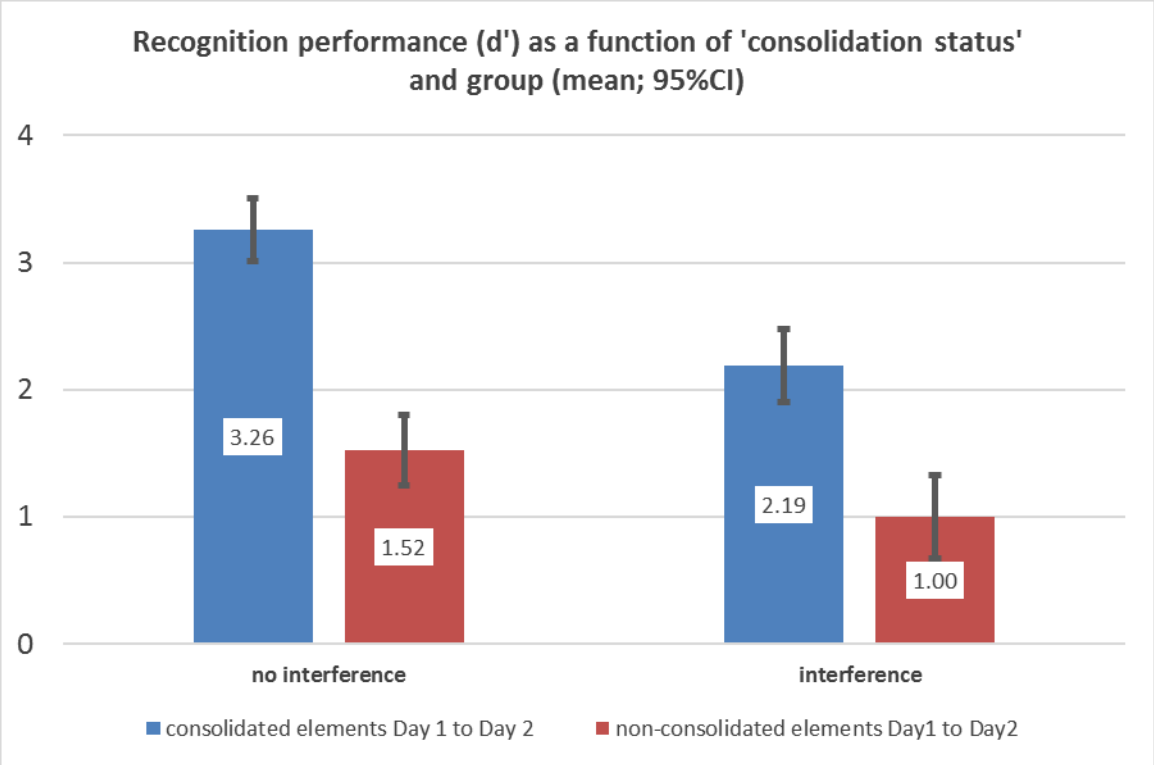

Figure 4.4. The effect of interference on consolidated items through the first two days by measuring recognition performance.

The results on the recognition test on Day 3 revealed a significant consolidation*group interaction effect ($F_{1,38}$=5.38, $p<0.05$) regarding the memory strength for the elements that were consolidated vs. non-consolidated across the first two days of the experiment, hence indicating that the Non-Interference Group showed a larger difference in the memory strength between consolidated vs. non-consolidated elements (D1-D2), than the Interference Group. While both types of elements were well discriminated for the Non-Interference Group (a significant difference from 1, a value which indicates as much noise as signal in individuals' memory),

only the consolidated elements were well discriminated in the Interference Group; non-consolidated elements were recognized closer to chance level.

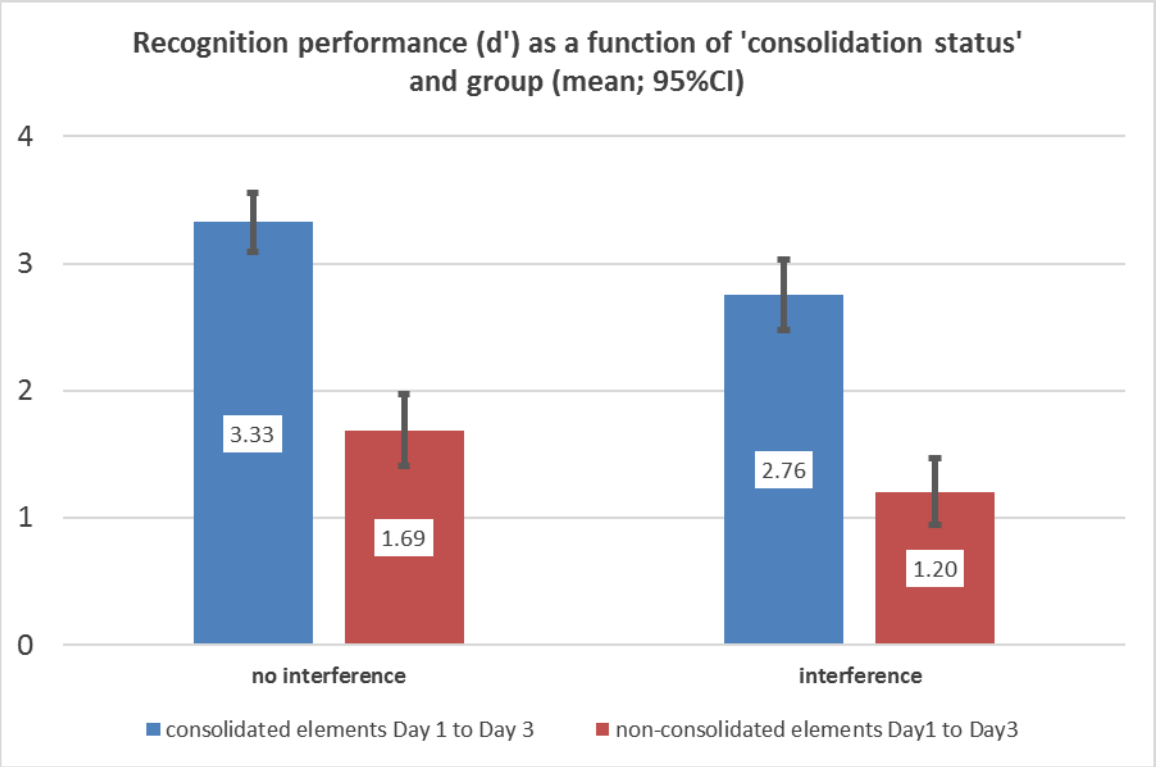

Figure 4.5. The effect of interference on consolidated items through the first two days by measuring recognition performance.

Even though we did not find a significant consolidation*group interaction effect ($F_{1,38}$=0.16, p=0.69) for the memory strength for the consolidated elements across all 3 days, we found a significant overall group difference (main effect: $F_{1,38}$=12.21, p<0.005) and a main effect of consolidated vs. non-consolidated elements ($F_{1,38}$=220.43, p<0.001). While both types of elements were well discriminated (a significant difference from 1, a value which indicates as much noise as signal in individuals' memory) in the Non-Interference Group, only the consolidated elements were well discriminated in the Interference group.

4.4 – Memory Consolidation, Reactivation and Reconsolidation

Assessing the effect of interference on the reconsolidation of consolidated vs. non-consolidated items may provide an answer to the question of whether the reconsolidation process is similar or different than the consolidation process (Figure 4.6).

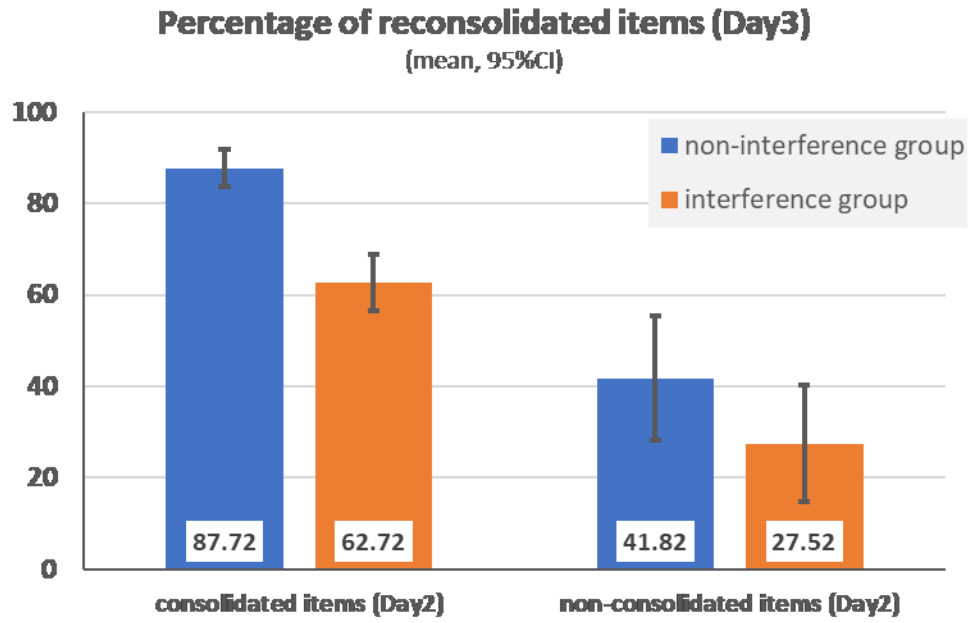

Figure 4.6. The effect of interference on reconsolidation of consolidated items on Day 2 by percentage of reconsolidated items.

The statistical analysis shows that there was a significant difference between the two groups only for consolidated items [$t(38)=6.903$, $p<0.001$], but not for the non-consolidated items [$t(35)=1.473$, $p=0.15$]. (The difference in the degrees of freedom between two tests comes from the fact that 3 participants in the interference group did not have non-consolidated items on Day2.) The results (Figure 4.7.) indicate that the consolidated items (i.e. encoded on Day 1 and expressed at retrieval on Day 2) were more sensitive to the interference manipulation than the items that were not consolidated (i.e. encoded on Day 1, but not expressed at retrieval on

Day 2). This finding supports the idea that the cued-retrieval test used to assess consolidation on Day 2 made the memory traces for the retrieved (i.e. consolidated) items more sensitive or vulnerable to interference presumably via their reactivation. For items were not retrieved (i.e. not reactivated), there was no significant effect of interference.

Using our operationalization of consolidation, reactivation and reconsolidation processes, we assessed, in each group, the proportion of consolidated/reactivated items (based on the recall performance on Day 1 and 2) that were forgotten, recalled by chance, put into a labile state, partially reconsolidated or completely reconsolidated (Figure 4.7).

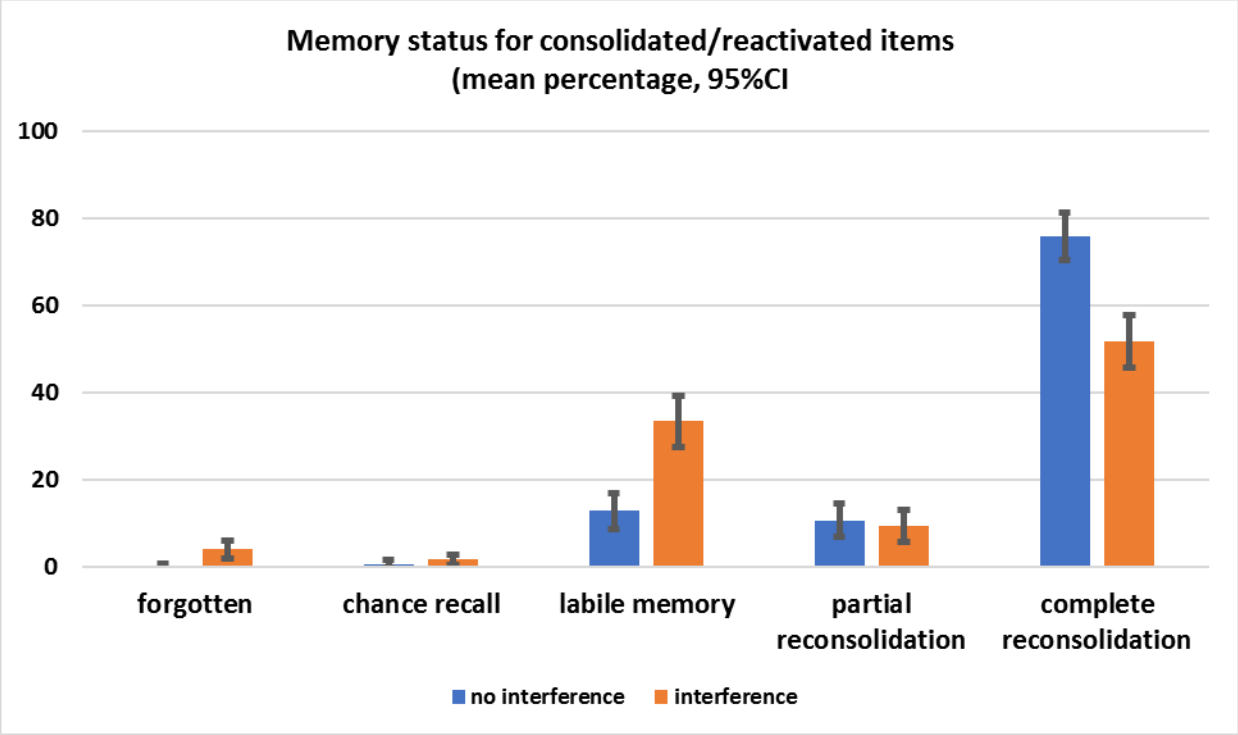

Figure 4.7. Comparing the memory status of consolidated items in both interference and non-interference group.

The mixed ANOVA analysis indicate that there was a significant memory status*group interaction effect ($F_{1,38}$=5.38, $p<0.05$), suggesting that the distribution of

consolidated/reactivated items based on memory status was different between the two groups. Pairwise comparison of the two groups for each memory status type showed that there were significant difference between the two groups for the forgotten items, those put into a labile state and those completely reconsolidated (all $p<0.05$, Bonferroni corrected) (section 3.4). Specifically, the Non-Interference group had a higher proportion of items completely reconsolidated than the Interference group ($p<0.005$), whereas the reverse pattern was observed for the forgotten items ($p<0.00$). It showed that the interference not only can have an effect on reactivated items, but also that the reconsolidation process is qualitatively different from the consolidation per se, with, presumably, different brain networks underlying these two processes.

Chapter 5 – Discussion

This project set out to investigate the reconsolidation of declarative memories (visuo-spatial associations), by using a classical three days experimental design in which we manipulated the memory reactivation and interference.

5.1 – Summary of results and discussion

5.1.1 – Memory performance

We observed a difference in the immediate recall performance of matrix A on Day 1 between two groups (Figure 4.1) despite the similar performance of participants from the two groups during the last loop of training and a similar number of loops to complete the training (Table 1). This results suggest either that participants in the two groups have different short-term or working memory retention skill level or that there was a difference in the encoding strength despite a similar performance at the last cued-retrieval block of training. This difference cannot be explained by possible particularities of the experimental design since the participants were not informed about their group assignment until Day 2 and there was a 10 minutes interval between the last training block and the immediate cued-recall test. Nevertheless, given that most studies using similar designs usually consider as baseline performance the results of the last recall test during training, our finding highlight the need for introducing a delay between the training and immediate memory testing. In any case, this difference was in favor of participants from the Interference group who, despite their superior performance at the immediate recall test, showed a significant worse performance at the cued-recall test of Matrix A on Day 3, after the

interference manipulation, thus confirming its powerful effect in impairing the memory performance.

Importantly for our study, despite the above-mentioned difference, the amount of forgetting, expressed as percentage loss from Day 1 to Day 1 relative to performance at the immediate recall test, was similar not significantly different between the two groups (Figure 4.1). This suggests the fact that memory traces were sensitive to the typical decay shown for associative memories (Cohn and Moscovitch 2007; Eichenbaum, Yonelinas et al. 2007; Sadeh, Ozubko et al. 2014) such as used in our study (between objects and the locations), to the same extent in both groups.

The overnight consolidation was expressed in our study as the percentage of items correctly recalled on both Day 1 and Day 2 and it was similar for both the Interference and Non-interference group (see Figure 4.3). In previous studies, such as that by Rasch and colleagues (2007), the consolidation was operationalized as the percentage of correctly recalled items overnight relative to the percentage of correctly recall items at the last run during learning, a measure that allows for values higher than 100% (Rasch, Büchel et al. 2007a). While this approach allows for the assessment of 'spontaneous gains', similar to those seen in studies investigating the sleep-dependent consolidation of procedural memory such as motor sequence learning, for a review see (Maquet, Laureys et al. 2000; Diekelmann and Born 2010), we believe that it may not be appropriate for the investigation of declarative memory for several reasons. First, in motor sequence learning studies, the dependent main variable is reaction time and participants make very few accuracy errors. As such, the gains that are observed, are gains in reaction time, not in accuracy. Second, researchers in declarative memory studies using the same approach as Rasch and colleagues do not distinguish between items that were recalled on both

Day 1 and Day 2, forgotten on both days, those that were forgotten on Day 2 after being recalled on Day 1 and items that were not recalled on Day 1, but were present on Day2. Thus, the memory decay process is not accounted for and the researchers have no means of distinguishing between items recalled by chance and those that were weakly encoded, but were strengthen by the overnight sleep. In contrast, in our study, the introduction of a 10-minute delay between the last block of learning and the actual memory test immediately after learning (during which participants filled out some questionnaires), ensures that the performance at the immediate recall test reflects accurately the memory encoding strength. Also, our measure of consolidation is more precise because it considers as consolidated only the items that were both well encoded after learning, as well as retrieved the next day. Finally, many reconsolidation studies using a 3-day experimental design do not even assess consolidation on Day 2, but they simply assume that it occurred (Forcato, Burgos et al. 2007; Forcato, Rodríguez et al. 2011).

Despite the difference in the absolute performance at the immediate cued-recall test on Day1 (i.e. number of items correctly recalled) between the two groups, the consolidation rate, expressed as percentage of these items that were also recalled on Day2, was similar in both groups. Given that different people may have different encoding skills, as illustrated by the very difference between groups, but also by the variability across individuals, the similarity in consolidation performance suggests that consolidation is a general process and that, regardless of the encoding amount, we tend to consolidate the same, in percentage.

The interference manipulation led to an impaired memory performance in the Interference group in both recall and recognition tests on Day 3. These findings are in line with previous reconsolidation studies, using a similar paradigm like ours, but only one type of memory test, that showed lower performance in interference group on the last day of testing, for

either recall or recognition tests (Hupbach, Gomez et al. 2007a; Forcato, Rodríguez et al. 2010; Hupbach, Gomez et al. 2013; Wichert, Wolf et al. 2013). Importantly, this phenomena was reported for other types of memories, such as procedural memory assessed by finger tapping learning task (Walker, Brakefield et al. 2003) or in fear memory (Schiller, Monfils et al. 2010), thus demonstrating that deteriorating effect of interference seen in reconsolidation studies is more a general process and not domain specific.

Evidence for the updating model in reconsolidation research comes from studies using two sets of material to be memorized and investigating the intrusion rates from one set to another, specifically whether these intrusions are unidirectional (indicating updating) or bi-directional (indicating source mis-identification). Indeed, several reconsolidation studies have demonstrated the updating of previously learned information by showing asymmetric intrusions from the new memory traces into the old ones (Hupbach, Gomez et al. 2011; Sederberg, Gershman et al. 2011). In our study, we have also observed intrusions from matrix B (newly learned material) into matrix A (old material) on Day 3 in the Interference group. However, by design, matrix B was always learned after testing the memory related to matrix A on Day 2, and the testing on Day 3 was always done first on matrix A, then on matrix B (to ensure that the time of testing of memory traces related to matrix A was the same in the interference and non-interference groups). As such, we could not conduct a proper analysis of intrusions that would have provided evidence for the updating model (Hupbach, Gomez et al. 2009) or for the source mis-identification (Johnson, Hashtroudi et al. 1993). In addition, given that in our study participants in both groups have always passed the cued-recall test before the recognition test, it is still an open question whether the order of these tests may have had any effect on the number of intrusion or false memories, seen in the Interference group.

The significant decrease of performance in recall test on Day 3 in the Interference group as compared with that of participants form Non-Interference group on Day 3 (see Figure 4.1), seems consistent with the hypothesis that learning new items has deleterious effects on previously acquired memories because the memory traces compete with each other, and the magnitude of this effect depends on the similarity between these competing memory trace, as posited by the interference theory (MacGeoch 1942; Underwood 1957). This negative interference effect on memory performance was shown for other type of materials, such as verbal (i.e. learning a list of words) and across various experimental conditions, that is, regardless of whether reminders or cues were used or not (Hupbach 2015). Any recognition test allows for the assessment of the degree of similarity/dissimilarity between competing memory traces via the d-prime parameter. In the analysis of the memory recognition test on Day 3, however, we used this parameter (based on hit rate and false alarm scores) as an indicator of memory strength. As expected, the memory discrimination was higher in the Non-Interference than Interference group, suggesting that the memory strength of items from matrix A was diminished in the latter by the interference from competing memories from matrix B. The same effect was previously reported in (Wichert, Wolf et al. 2013) study, in which it has been shown that memory accuracy was reduced on day 15 in subjects who had learned new material on day eight of the experiment, by using d-prime as measurement. One possible explanation for why the Interference group in our study has performed worse in the recognition test than the Non-Interference group is that there was another memory reactivation during cued-recall of matrix B on the third day, which took place before the recognition test that could have made memories labile and not strong enough to be discriminated. However, there are studies in which there was

no impairment (or enhancement) in the performance of a memory recognition test that was administered after a recall test (Singh and Rothschild 1983).

Comparing the recall performance for consolidated items (i.e. items correctly recalled in both day one and day two) we did not observed a difference between Interference and Non-Interference groups. However, in regards to performance across all three days of testing (i.e. items correctly recalled in each day), we found a significant difference between the two groups. This pattern of reduced performance due to interference, but only at the level of the consolidated items is shown here for the first time in the reconsolidation literature, to the best of our knowledge, and it provides direct evidence that consolidated items were indeed reactivated on Day 2 (prior to interference).

Unlike any previous study investigating reconsolidation, our design allowed us to compare the memory strength of consolidated and non-consolidated items in both experimental groups either for the first two days or for all days of the experiment (i.e. items correctly recalled on Day 1 and 2 versus items correctly recalled in all 3 days). For this purpose, we used again the d-prime parameter, this time just for consolidated items on the first two days versus non-consolidated items. We found a bigger difference in d-prime in the non-interference group as compared to the interference group indicating that these subjects were able to better discriminate consolidated items versus non-consolidated ones. In the interference group even though there was a difference in discriminating between these items, we found that the d-prime for the non-consolidated items was at chance level. The same pattern of results was found when we considered the consolidated vs. non-consolidated items across all 3 days. It is worth noting that even though the non-consolidated items have not been recalled in both Interference and Non-Interference groups, only the non-interfered subjects were able to discriminate more than at

chance level the non-consolidated items. For these items, we may assume that there were memory traces that were still active in short-term memory, but that they were weak and cannot be retrieved, which is in line with the model proposed by the decay theory (Peterson and Peterson 1959).

5.1.2 – Recognition failure of recallable items

When the subjects are able to recall items that they could not recognize, this is called recognition failure of recallable items, a phenomenon that was described previously in the recognition literature (Tulving and Osler 1968; Thomson and Tulving 1970). The generate-recognize theory assumed that there is a dependency between recall and recognition test and that a successful recall is dependent on a successful recognition (Watkins and Gardiner 1979). However, other researchers have reported studies in which there was a correct recall despite the failure to recognize a specific item (Tulving and Thomson 1973; Watkins and Tulving 1975), thus rejecting the generate-recognize theory (Watkins and Gardiner 1979; Tulving 1983). This finding has been seen frequently in cued recall paradigms, which was the case of our study. Interestingly, in contrast to previous studies investigating this phenomenon (Gardiner 1988), we employed the recognition test after and not before the cued-recall. Based on our continuum of classifying the items based on the memory strength (section 3.6.3), we put these items in the category "recalled by chance" and we found no significant difference between Interference and Non-Interference group in the percentage of consolidated items falling in this category. The fact that the interference did not seem to affect the items in this category seems to confirm our classification, because these items would have not been well encoded; however, it is also very

difficult to draw definite conclusions about them, given that there were very few items in this category.

To our knowledge, there is no previous study using both recall and recognition tests in order to assess the recognition failure of recallable items for different types of memory like associative forms of spatial memory. By using only one type of memory test, we could either include these items among the consolidated/reconsolidated (because they are present at recall), or consider them forgotten (since they are absent in recognition). In either case, the classification would not be appropriate, hence the importance of having both types retrieval tests in a study, if the design allows it.

5.1.3 – Retrieval practice

One of the memory enhancers is the retrieval practice itself, given the evidence that each memory testing session occurring after learning improves the long-term memory more than extended repetitions within the same learning session (Roediger and Karpicke 2006b; Roediger and Karpicke 2006a). In addition to enhancing long-term retention, retrieval practice was found to protect memories from proactive interference or intrusion of retrieved memory into subsequent new items (Weinstein, McDermott et al. 2011; Grimaldi and Karpicke 2014). Only a limited number of studies in the reconsolidation literature have used repeated cued-recall tests across multiple sessions, each of which can be seen as retrieval practice (Walker, Brakefield et al. 2003; Halamish and Bjork 2011; Potts and Shanks 2012). In our study, learning of new association between objects and locations as part of matrix B caused impairment in the recall of items from matrix A, as well as reduced performance in the recognition test in the interference group. Moreover, the worsening of the recall scores of matrix A on Day 3 as compared to Day

2 in the Interference group (Figure 4.1) suggests that having the recall test on Day 2 (i.e. retrieval practice) did not prevent retroactive interference (RI) on Day 3 (interference of newer information with retrieval of previous memory traces). Given that we did not have a recognition test for matrix B, we could not confirm previous reports that retrieval practice protects against proactive interference, but we provided evidence that it does not protect against the retroactive interference. Moreover, the differential effect of interference on the reconsolidation of consolidated vs. non-consolidated items (Figure 4.6) supports the idea that the cued-retrieval test used to assess consolidation on Day 2 could not prevent the RI because the consolidated items became more sensitive or vulnerable to interference presumably via their reactivation. This finding contradicts results from a previous study in which improvement of original memory was shown regardless of the presence/absence of interference, whenever reminders were employed, showing that reminder testing, rather than retrieval practice per se, had a protective role for memories against interference (Potts and Shanks 2012).

Strength of memory is one of the factors that can affect the modification of memory during reconsolidation (Eisenberg, Kobilo et al. 2003; Suzuki, Josselyn et al. 2004) . In our study, during encoding, the matrix A was repeated between two and eight times in order for our participants to reach the learning criteria set prior to the task. This number was similar (between two and six times) for matrix B on the second day, for participants in the Interference group. Even though these participants reached the learning criteria for both matrices, they may still have had different encoding strengths for different items, as indicated by the group differences at the immediate recall. Regarding the reconsolidation and the memory strength at encoding, we did not find any relation between the memory performances on Day 3 either at recall or

recognition tests and the strength of memory at the training session (based on the number of loops needed to reach learning criteria).

5.2 – Advantages of our experimental paradigm

5.2.1 – Assessing the memory strength

Assessing the strength of memory traces by combining the performance at recall and recognition test on the final day of the experiment is the innovation brought about by our study in the reconsolidation research. We developed a spectrum for the strength of the reconsolidated memory traces ranging from forgotten to reconsolidated, which we applied only to the items that were already consolidated (conceptually, we cannot consider reconsolidation for items that were not consolidated in the first place). Previous studies in reconsolidation research either used recall (Forcato, Burgos et al. 2007; Hupbach, Gomez et al. 2007a; Hupbach, Hardt et al. 2008; Forcato, Argibay et al. 2009; Hupbach, Gomez et al. 2009; Forcato, Rodríguez et al. 2010; Hupbach, Gomez et al. 2011) or recognition (Wichert, Wolf et al. 2013a; van Schie, van Veen et al. 2017), alone.

This spectrum allowed us to assess how interference can affect memories of different strengths; specifically it allowed us to assess whether there were significant differences between interference and non-interference group for memories that were forgotten, labile or completely reconsolidated. By showing that Interference and Non-Interference group had different proportion of items in these categories we have demonstrated that the interference not only can have an effect on reactivated items, but also that the reconsolidation process is qualitatively

different than the consolidation per se, with, presumably, different brain networks underlying these two processes.

5.2.2 – Model for reactivation studies in future research

In previous studies in the reconsolidation literature, the researchers made assumptions that reactivation occurred. For instance, Forcato and Hupbach did not test the memory on the second session of their experiment as the prove if the memory was consolidated or not (Hupbach, Gomez et al. 2007a; Forcato, Rodríguez et al. 2010) and they used reminders that presumably elicited memory reactivation. In our study, in contrast, we provide direct evidence for reactivation by conducting our reconsolidation analysis only on items that were consolidated (i.e. recalled in both Day 1 and 2), hence on items for which we know that reactivation occurred on the second day. Other studies have also used recall as a mean of reactivating the memory trances and showing the extend to which various items were consolidated (Wichert, Wolf et al. 2013), but the effect of interference was tested on the whole memory, not just on consolidated items. Having both criteria in our study, provided us with the direct evidence that reactivation occurred. It is also important to consider that, conceptually, we cannot assume to have memory reconsolidation without demonstrating that memories are consolidated in the first place and then, that they are reactivated. Our approach could be a potential model for future research on reconsolidation.

5.2.3 – Short term versus long term memory

As our intention was to test long-term memory and not to assess the working memory, we decided not to test the encoded elements immediately after learning and we introduced a five

to ten minutes delay between encoding and recall. Moreover, we employed an algorithm that randomized the order of item presentation during each learning block (loop). By using this approach, we avoided the recency effect, which is typical for short-term memory. The same approach has been used for the immediate recall in (Sonni and Spencer 2015) study, in which there was a 20 minutes of gap between encoding and the recall test that was used as the baseline memory score. In contrast, other studies, such as Rasch (2007), did not separate the immediate retrieval from the end of encoding, and used the last run of cued recall during learning as the baseline (Rasch, Büchel et al. 2007a). By avoiding the recency effect, we believe that our results reflect more appropriately the long-term memory capacity, rather than that of working memory, an issue that should be considered in future research in this area. Moreover, this issue highlight the importance of choosing an appropriate baseline against which to assess the magnitude of the consolidation or reconsolidation measurements.

5.2.4 – The visuo-spatial association task

The task that we develop in the current study offers two key advantages as compared with other types of tasks used in the consolidation/reconsolidation literature. First, it allows for the analysis of memory strength at the individual item level. Specifically, in addition to the usual binary outcome in the cued-recall test (correct/wrong), the wrong responses can also be quantified in terms of the spatial distance from the correct response within the matrix. Second, the same feature (i.e. distance between the positions of two items within the matrix) it offers researchers the possibility of either manipulating the similarity between two different matrices in interference paradigms or a quantitative assessment of intrusions from one matrix to the other, also at the individual item level.

5.3 – Limitations

As it is the case with any research, our study has several limitations.

One limitation may arise from the fixed order in which the recall and recognition tests were administered in the last day of our study, given that past studies have shown that memory performance may be affected by this factor. For example, Postman et al. found that the recall performance was improved by a prior recognition test, whereas a recall test had a depressive effect upon the performance for a subsequent recognition test (Postman, Jenkins et al. 1948). This effect had been confirmed by later studies, as well (Belbin 1950; Hanawalt and Tarr 1961). In our study, on Day 3, there were three memory tests with a fixed order (recall of matrix A, recall of matrix B, and recognition of matrix A) for the interference group as opposed to just having a recall test of matrix A and the recognition test for the non-interference group. As such, in both groups, recall tests preceded the recognition test, presumably weakening the memory performance for the latter test for all participants. However, having an extra recall test in the interference group could have impacted the discrimination ability of these subjects in the following recognition test, even though we had the same amount of time between recall of matrix A and the recognition test for both groups. In retrospect, we could have assessed or control for this order effect by adding another interference group in which the recall test of matrix B was administered after the recognition test.

Regarding the impact of the interference manipulation, it would have been interesting to have another recognition tests in addition to the recall tests on all days of experiment, but specifically on the second day of the study, in order to assess the memory strength of the consolidated items before the interference. However, we do not know to what extent this

recognition test would have impacted the memory reactivation or the reconsolidation process *per se*.

Unlike other previous studies using recognition paradigm (Singh and Rothschild 1983) (Squire, Wixted et al. 2007), we did not combine the forced choice binary recognition with a confidence test, in which participants can express their level of confidence in the making their choices. The addition of the confidence test would have provided a better insight into the labile memory category, especially in regards to the recognition failure of recallable items, thus having a better understanding of the reconsolidation process.

5.4 – Conclusion and future implications

In summary, this work studied memory reconsolidation from various aspects. It was based on the fact that memory reconsolidation opens the way for modification and disruption of memory traces through opening them after reactivation. Despite the limits mentioned in the previous section, the results of this project provided verification and validation of this model in the form of a proof-of-concept study. It provided direct evidence for the effect of interference on reactivation of declarative memories by using an innovative experimental paradigm in healthy young adults.

Apart from its impact on learning and quality of life, as well as the shaping of between humans and their environment (Brem, Ran et al. 2013), the modification of memory via reconsolidation during psychotherapies targeting memory reframing could be used for treating clinical disorders like anxiety (Kindt and van Emmerik 2016; Beckers and Kindt 2017) and trauma (PTSD) (Gray and Bourke 2015). As such, the in-depth investigation of the memory reconsolidation process can have an important impact with critical clinical applications.

This behavioral study opens the way to distinguish the anatomical substrate responsible in the consolidation and reconsolidation of declarative memory using functional magnetic resonance imaging (fMRI). Therefore, it enables a path to study potential neurophysiological correlates of memory consolidation during sleep.

In this research work we have shown the technical feasibility and validity of this concept. For the next step it would be desired to move on to the prototype step for further validity and planning for the pilot phase of the project.

I am deeply dedicated and committed to continue this work until its realization in enhancement of quality of life of the public and people of our society.

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